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GASTROENTEROLOGY

Official Journal of the American Gastroenterological Association

VOLUME 3 | *SEPTEMBER 1944* | NUMBER 3

INTUBATION STUDIES OF THE HUMAN SMALL INTESTINE

XXIV. A Review of a Ten Year Experience[1, 2]

T. Grier Miller, M.D.
Philadelphia, Pa.

INTRODUCTION

When I accepted the very kind invitation of your committee to deliver this annual Lewis Linn McArthur Lecture I did not know that it was a surgical lectureship. Under the circumstances, I would now be much embarrassed if I did not appreciate that the honor you have done me, as an internist, is an indication that today, except in respect to certain technical aspects of therapy, the approaches of the surgeon and of the internist to their special problems are fundamentally the same. So long as the internist regarded certain diseases as strictly medical and responsive only to drug therapy and the surgeon looked upon other diseases as intrinsically within his field and amenable only to some operative procedure, the two had relatively little in common. As investigations into the nature of disease processes and the resultant bodily reactions have proceeded, however, much overlapping and identity of interest have been discovered. Both the surgeon and the internist have found it necessary to understand the primary causes of disease, its natural history, its pathological physiology and its response to various types of treatment, whether that be drug therapy, psychotherapy, chemotherapy, radiotherapy or some operative procedure.

On such a basis, I take the liberty of assuming that you may be interested in certain investigations that have been under way in our Gastro-Intestinal Clinic at the University of Pennsylvania Hospital for the past ten years. They have grown out of a technique for intubation of the small intestine, and, more or less by chance, have led to a procedure of some practical importance in the management of patients with intestinal obstruction. I shall deal more especially, however, with the research aspects of the work, and wish first of all to state that the major credit for the results is due to my associates: Fellows of

[1] From the Gastro-Intestinal Section (Kinsey-Thomas Foundation) of the Medical Clinic, Hospital of University of Pennsylvania.

[2] Presented as the Twentieth Lewis Linn McArthur Lecture of the Frank Billings Foundation of the Institute of Medicine, Chicago, May 26, 1944.

our own School and some temporarily assigned to our Clinic by the Medical Schools and Hospitals of Harvard, Yale, Western Reserve, Maryland, Duke and Virginia Universities, and the members of our permanent staff, including Walter G. Karr, Kendall A. Elsom, Thomas E. Machella, Joseph T. L. Nicholson and especially the late William Osler Abbott. The latter, as the senior of the group, continuously supervised the research and was responsible for many of the technical procedures, and he also, with Charles G. Johnston, later of Wayne University, first applied intestinal intubation in the treatment of the patient with an obstructed bowel.

My personal interest in the physiology of the small bowel dates back to 1913, just after my interneship, when first, I read Arthur Hertz' (1) (now Hurst) fascinating little book on "The Sensibility of the Alimentary Canal," in which he detailed his investigations on the causes of digestive symptoms, with special reference to the esophagus, stomach and rectum; second, Carlson's then current articles on his studies of the motor functions of the stomach, and third, Einhorn's papers on intubation of the duodenum. It occurred to me that similar observations on the small bowel might be made. Though not adequately trained in physiology, and lacking the facilities of a laboratory, I then undertook, with the Einhorn duodenal tube, to intubate the jejunum and to study its contents. I knew of Cannon's observations on the motor function of the intestine by the roentgen ray, but I did not know at the time that in 1908 Scheltema (2) had already accomplished so called "permeation" of the entire tract in children for treatment purposes. My experiments were not very successful, but I continued to be interested in the subject, and when in 1919 Einhorn (3) published a description of his jointed tube for the treatment of colon infection I again made some effort, with his new tube, to secure samples of juice from the small intestine for chemical and microscopical study. With this apparatus, however, several days were required to reach the lower portions of the small bowel, and the lumen of the tube was so small that satisfactory specimens could not be obtained.

I did not take up the problem again until about 1932, when our Gastro-Intestinal Clinic had been organized, and a small fund became available for research purposes. Fortunately, at that time Abbott, who had been trained in physiology under A. N. Richards, was associated with me and was attempting some experiments in man on the effects of drugs on the duodenum. He was employing an Einhorn duodenal tube with an inflatable balloon attached to its distal end, and making kymographic records. His experiments, however, were unsuccessful because each time he examined the subject under the fluoroscope he found that the balloon had shifted its position. It was always going lower and lower in the bowel. Then, in the midst of his frustration, it occurred to me that we might attach to his tube just above the balloon another

similar one, with apertures near its distal end, and watch the progress of the apparatus under the fluoroscope. The result was that within a few hours the balloon, followed by the two tubes, had reached the cecal area, and through the attached open tube we (4) were able to secure satisfactory intestinal specimens. We did not then know that already Chester Jones (5), in Boston, had frequently introduced a similar tube, with an attached balloon, for the purpose of studying referred pain from the intestine; he, however, had not provided a means of aspirating intestinal contents. It remained for us only to secure a doubled-lumened tube of sufficient length to reach the cecal area, one lumen for distension and deflation of the balloon, the other for aspiration or injection purposes. That was not easy because a double-lumened rubber tube of such length had not previously been manufactured, and it was a year before we were able to induce any business organization to undertake the experimental procedure. Thus, one may say that largely by accident and some patience intestinal intubation as a practical technique became established.

PRELIMINARY OBSERVATIONS

The technique of intubation obviously permits many investigations of small intestinal function, but first of all we were interested in attempting to determine in man certain physical and chemical facts regarding the fasting contents at various levels and the influence of certain factors on the characteristics of the fasting contents. Although many such facts had previously been determined for animals and, under abnormal conditions, for man, we felt that they did not necessarily apply to man with an intact and normally functioning digestive tract.

For these preliminary studies the tube was introduced with the subject in a fasting state, and when the balloon reached certain predetermined areas it was deflated and a sample of the normally flowing fasting contents was aspirated. These areas, identified in each instance by the fluoroscope, were the duodenum, the jejunum, the upper and the lower ileum. Each specimen was collected under identical conditions, in a closed system of tubes, at a fixed negative pressure, and, when possible, one after another as the tube was allowed to pass downward; in some instances only one or two specimens could be collected on a single intubation. The data on the samples from each area were assembled and averaged. The physical characteristics of the aspirated material, its rate of flow in and from the bowel, its chemical reaction and its chloride and bicarbonate concentration were determined; sometimes also the calcium and phosphorus concentration, and occasionally the total base.

On the basis of such data on fasting specimens obtained by 51 intubations in 30 normal subjects, Karr and Abbott (6) found that the rate of flow of the contents averaged less than 1 cc. per minute; that the reaction, though usually

acid in the duodenum and sometimes so in the jejunum, was essentially neutral throughout the ileum, and that the osmotic pressure (estimated by the addition of the chloride and bicarbonate ions), though lower in the duodenum, tended in the jejunum and ileum to be the same as that of the blood plasma (about 300 milliosmoles).

Their work, supplemented by that of Miller and Karr (7), showed, however, that these conditions were altered when various solutions were orally administered before the intestinal collections were made. The latter workers took into consideration the factor of gastrointestinal motility, measuring it by means of a dye (vital red) introduced with the test material. The administration of water or a gelatin solution promptly increased the rate of flow in the vowel and, in cases of hyperchlorhydria, markedly reduced the pH of the intestinal contents as the acid gastric secretion reached the area (indicated by the appearance of the dye). When, however, in a normal subject a highly acid or alkaline solution was administered the motility was not greatly increased and the neutral reaction of the ileac contents was not affected. In spite of these observations a weakly alkaline solution passed rapidly from the stomach and produced a slightly alkaline reaction in the intestine, this probably explaining the laxative effect of a small dose of sodium bicarbonate in some persons. It would seem, therefore, that the reaction of the intestinal contents is governed by the reaction of the gastric contents and by the speed of their evacuation from the stomach. So long as the emptying of the stomach is slow, no matter what the reaction of its contents, the reaction of the contents of the intestine tends to remain approximately neutral, but when the gastric acidity is high and evacuation rapid some increase in the acidity of the intestinal contents occurs.

We have already observed that the osmotic pressure of the fasting jejunal and ileac contents tends to equal that of the blood plasma; even after the oral administration of water or strongly alkaline or acid solutions this phenomenon tends to persist. And yet it must be remembered that two factors are constantly at work to reduce the osmotic pressure of the duodenal contents: (1) the inflow of gastric contents which usually are hypotonic, and (2) the process of neutralization that begins as soon as the acid gastric contents enter the duodenum. Even if the gastric and the duodenal contents separately are isotonic their combination reduces the osmotic pressure by 50 per cent. The sodium of the sodium bicarbonate of the duodenal fluid combines with the chloride of the hydrochloric acid from the stomach to form sodium chloride, which has a pressure of just one half either of the original fluids, while the resultant CO_2 is readily absorbed. The resultant state of hypotonicity, however, tends to be overcome by the absorption of water from the bowel and by the diffusion of salt into it. And yet if the motility is very rapid, as after the oral administration of water, the osmotic pressure, even of the ileac contents,

may be somewhat hypotonic. On the other hand, if a strong bicarbonate of soda solution is administered orally there is some tendency toward a transient hypertonicity in the duodenum and jejunum, but not in the ileum.

The maintenance of isotonicity seems to depend chiefly on a reciprocal relation between the chloride and the bicarbonate ions, the chloride especially passing back and forth through the intestinal wall in accordance with the amount of bicarbonate present so that the two added together usually produce an osmotic pressure of approximately 300 milliosmoles.

EXPERIMENTS WITH GLUCOSE

These observations on the electrolyte factors of the intestinal contents led naturally to some experiments on the influence of food substances. Because it seemed to be the simplest one, because it would probably influence other factors that control the osmotic pressure, and because much work with it had been done previously in animals, glucose was chosen for the first investigation. The analagous work on animals by Magee, Cori, Pierce, Verzar and McDougall and Ravdin, Johnston and Morrison have had a direct bearing on this problem.

By sampling the bowel contents at various levels after the oral administration of 5 to 50 per cent solutions of glucose Abbott, Karr and Miller (8) found that, irrespective of the strength of the administered solution, the concentration in the jejunum and ileum rarely exceeded 5.4 per cent, which constitutes isotonicity with blood plasma. Usually, and always in the ileum the concentration was sufficiently less so that, even with the added increments of the electrolytes, the total osmotic pressure did not exceed 300 milliosmoles. A reciprocal relationship between the glucose and the electrolytes immediately established itself, the electrolytes increasing or decreasing in accordance with the amount of glucose present.

At times, however, as after the administration of a large amount of a highly concentrated sugar solution, hypertonic contents appeared in the jejunum. Since such a hypertonic condition never developed in the ileum it seemed probable that one or more of three compensatory factors in the small bowel were responsible: absorption, dilution and rapid dispersion.

In order to study this matter further Abbott, Karr and Miller (9) isolated a segment of the jejunum between balloons, using a three-lumened tube, and through the third lumen injected the test solution and aspirated the resultant contents after a fixed period of time. In regard to the volume, they found that when the concentration of the injected glucose solution exceeded 5 per cent the volume of the contents after fifteen minutes had increased considerably; furthermore, that the amount of increase varied directly with the increase in concentration of the injected solution. On the other hand, when the concentration was below 5 per cent (hypotonic) the volume after 15 minutes actu-

ally decreased. Thus dilution at least is one factor that tends to reduce the concentration.

In regard to dispersion, some data were obtained by making kymographic records from the balloons at the two ends of the segment. The tracings showed clearly that after the injection of a hypertonic solution peristalsis became far more active, thus indicating an effort to disperse the contents quickly and so permit further dilution and absorption.

Because of the mangitude of the factors of dilution and dispersion, it was impossible, in the isolated segment, to measure absorption from a hypertonic solution, but when a hypotonic solution was injected, it was easily demonstrated that absorption varies directly with the degree of concentration. That the same thing occurs with hypertonic solutions had previously been demonstrated in animals by Verzar and McDougall (10), also by Ravdin, Johnston and Morrison (11).

Thus it is evident that as glucose enters the gut a normal osmotic pressure is maintained by 1) a displacement of the chloride and bicarbonate ions, 2) an inflow of hypotonic fluid, 3) dispersion of the contents and 4) absorption of the glucose.

In addition to these methods for the preservation of normal conditions within the bowel after the admission of a hypertonic solution, Magee and Reid (12) have shown that nature employs at least one other procedure: an outpouring of mucus that acts as a blanketing layer between the mucosa and the irritant material.

BEHAVIOUR OF GLUCOSE IN STOMACH AND DUODENUM

Because, however, nature has provided these means for combatting the presence of a hypertonic solution in the bowel and bringing about an isotonic state, one cannot assume that they are strictly physiologic. Under ordinary circumstances hypertonic solutions do not gain entrance to the bowel, especially the ileum. And yet, highly concentrated glucose solutions not infrequently enter the stomach. This led to a consideration of the means by which the concentration under physiologic conditions is reduced before the ileum is reached, to studies on the behavior of glucose in the upper digestive tract.

By means of two tubes, one two-lumened and one three lumened, Karr, Abbott, Hoffman and Miller (13) were able to devise an experiment in man that permitted an objective demonstration of what happens. Each of the five lumens had apertures at a different area: mid-stomach, pyloric antrum, duodenal cap, mid-duodenum and the first portion of the jejunum. From all of these areas aspirations could be made simultaneously. By making such aspirations after the oral administration of glucose solutions of varying concentration, they showed that, irrespective of the strength of the solution in the

stomach, it usually was reduced to 15 per cent or less before it reached the mid-duodenum and to less than 6 per cent before it reached the jejunum.

This concentration in the duodenum is essentially that which Auchinachie, Macleod and Magee (14) showed was most favorable for passage through the excised gut of an animal (13.5 per cent) and which Magee and Reid (12) showed was most readily absorbed from the stomach in vivo. Indeed, by measuring the amount of sugar ingested and the amount recoverable from the bowel at the duodeno-jejunal level, our workers found that in man the greater part of it was absorbed before the jejunum was reached. Absorption above the jejunum, therefore, is obviously one of the ways by which nature prevents a hypertonic glucose solution from reaching the small bowel. This observation, incidentally, indicates the effectiveness of carbohydrate feedings in obstruction when only the stomach and duodenum are available for absorption.

In addition, however, Abbott, Karr, Glenn and Warren found another mechanism at work in the duodenum, that of dilution. By isolating the duodenum in trained subjects and introducing the glucose directly into the upper part of that organ they were able to demonstrate for a hypertonic solution not only marked duodenal absorption but also a marked increase in the volume of the contents.

In the stomach also dilution occurs in response to the intake of a hypertonic solution, but the matter of absorption in that organ is probably not such an important factor. Many workers have claimed that no absorption of sugar occurs in the stomach, but others, apparently the majority, feel otherwise. Shay and his co-workers (16) favor the latter view. Occlusion of the pylorus is exceedingly difficult in man, but Warren et al. (17), by using a double-balloon technique, were able to accomplish it in a few well-trained subjects. By that direct method they demonstrated that the amount of sugar disappearing from the stomach after variable time intervals is small as compared with that from the duodenum, and that such absorption as does take place occurs soon after the introduction of the sugar. Presumably some of the glucose that reaches the gastric wall in a hypertonic solution is absorbed, but the remainder soon becomes diluted by the passage of fluid from the stomach wall and this interferes with further absorption. At the same time the glucose in the center of the stomach may remain quite concentrated, this slowly reaching the wall for dilution as the contents near the wall are passed on into the duodenum. Thus, in the stomach dilution rather than absorption would seem to be the major factor in reducing the glucose to a suitable concentration for passage into the duodenum.

These observations with reference to the dilution of glucose in the stomach doubtless account for the feeling of fullness that so commonly is complained of by patients after the ingestion of an excessive amount of sugar. It is the

reason for the practice of avoiding sweet foods at the beginning of a meal, of having dessert at the end.

INTESTINAL ABSORPTION

From the beginning of our work Abbott and I were interested in the development of a satisfactory technique for the study of absorption from the intestine. The methods dependent on blood concentration, such as that used by Althausen (18) for galactose absorption, obviously are unsatisfactory because they cannot account for the material absorbed but later lost from the blood by utilization, storage and excretion. The difference between the amount of a substance ingested and that excreted in the feces is not a measure of absorption because it fails to account for possible absorption and subsequent excretion back into the digestive tube. The use of a segment isolated between balloons, such as we employed at first, was quickly abandoned not only because of the interfering dilution and dispersion factors, but also because the proximal balloon interferes with normal peristalsis and at the same time eliminates an admixture of the test substance with the normal secretions coming down from the stomach, liver and pancreas. Then Groen (19), working in Boston in Minot's laboratory and using our single ballooned apparatus, tried the injection of the test material immediately above the distended ballon and its removal by the same apertures after a fixed period of time. This was a distinct improvement and led to some interesting results, but it disturbed physiological conditions by necessitating regurgitation within the bowel and by distorting the ratio of volume to mucosal surface.

A more physiologic technique was eventually evolved by Nicholson and Chornock (20), who introduced the test material through one lumen of the double-lumened tube into the duodenum or jejunum, where it would come into contact in normal fashion with the duodenal secretions, flow with them to a fixed point down the tract and then be removed through the other lumen of the tube as the mixture arrived above a moderately distended balloon. They also devised, at Abbott's suggestion, a method of quickly terminating the experiment by injecting a magnesium sulfate solution through the proximal apertures and so within a few minutes washing out all the residual material from the segment. Theirs is actually a perfusion technique and allows selection of any desired portion of the intestine for the study, regulation of the flow of the material to be tested, maintenance of the normal secretory and motor functions of the bowel and exact timing of the exposure of the test material to the mucosal surface. By slowly and continuously injecting a 10 per cent glucose solution into the duodenum and collecting the residue as it arrived at a point low in the jejunum they found that for each half hour period about half of the sugar had been absorbed; furthermore, the subsequent washings, after the magnesium sulfate had come through, showed only mere traces of sugar.

Using the same technique they studied ascorbic acid absorption in a duodenojejunal segment and demonstrated in 19 separate experiments that within an hour this part of the intestine was capable of absorbing more than the optimal requirement for a 24 hour period. Then Moseley (21), one of our Fellows, applied this method to a study of the effects of the thyroid hormone on galactose absorption. Unlike Althausen, who used less direct methods, he secured entirely negative results. The technique also affords an opportunity to study more directly absorption defects in various affections of the digestive tract, including the liver and pancreas, and the effects of vitamins and other hormones on the absorption of carbohydrates, proteins and fats.

Before most food substances can be absorbed, however, they must undergo a certain amount of digestion within the tract. It seemed desirable, therefore, to have some direct method by which this process could be investigated. This problem was undertaken by Elsom, Chornock and Dickey (22). They eventually designed an apparatus that can be attached to the intestinal tube and into which food material can be placed for exposure to the intestinal secretions at any desired area and for any determined period of time. It consists of a short, thin brass tube that houses a perforated brass cylinder, the latter being temporarily sealed off by paraffin but capable of being opened at will within the bowel. Having introduced a weighed amount of solid food, such as beef, into the cylinder before it is swallowed, therefore, it is possible to withdraw the apparatus at any time after the secretions have been allowed to enter and, by subtracting the residue, to determine to what extent liquefaction of the original material has taken place. By this method they have as yet been able to make only some very preliminary studies on proteolytic digestion, but the technique would seem to deserve further attention, particularly in patients with pancreatic and hepatic disease.

DRUG EFFECTS

The technique we have used also affords an opportunity to study in man the effects of drugs on intestinal functions. Morphine has long been known to delay intestinal motility, but the mode of its action in this respect, as based on experiments in animals and to some extent in man, has not been clear. Some workers, including Magnus, as a result of roentgenological studies have thought that the impaired motility is due to inactivity and relaxation of the bowel, whereas others, including Plant and Miller, Gruber and Robinson and Orr and Carlson, on the basis of intraintestinal balloon experiments, have stated that the drug produces this effect by increased contraction. Either functional change obviously could explain a delay in motility.

Abbott and Pendergrass (23) employed both methods in man, and their results were of such a nature as not only to explain the disturbance of function but also to account for the divergent views previously held. By means of

kymographic tracings obtained simultaneously from balloons placed at various points in the bowel and of roentgenological observations made at the same time, they showed that the maximal effect of morphine, in the ordinary therapeutic dose, is on the second portion of the duodenum. From 2 to 20 minutes after its administration subcutaneously they found marked contraction of this portion of the duodenum, this being sufficient, without any pyloric spasm, to delay gastric evacuation, to empty a retained balloon of its air content and to push a barium mixture onward into the jejunum. At the same time they found that under these circumstances both the large peristaltic and the smaller segmentation waves of the duodenum are obliterated. Following this short period of increased motor activity, they found that the duodenum relaxes. This period of relaxation lasts as long as three hours.

They found similar but less marked changes in the jejunum and ileum. On roentgenographic investigation, furthermore, they observed that often, for 2 or more hours after the injection, a barium mixture in the small intestine, instead of being evenly distributed, is collected in agglomerations simulating large opaque sausages, the "moulage sign" described by Kantor as characteristic of sprue. Sometimes these masses had a haustrated appearance like that of the colon. This work in our clinic, therefore, showed that morphine first produces contraction of the bowel and then a prolonged period of relaxation. Most of the previous studies, especially those on animals, had been too brief to demonstrate the period of relaxation, whereas the roentgen studies, being more prolonged, showed mainly the secondary phenomenon of relaxation.

In view of the significance of the results with morphine Elsom and Drossner (24), also of our group, applied the same technique to a study of atropine. They confirmed its well-known depressant action on the motor function of the duodenum, jujunum, ileum and colon, and showed that this led to a decrease in motility throughout the small bowel. Since atropine is known to delay gastric evacuation it was thought that this might account for the delayed motility lower in the tract, but when the barium mixture was introduced directly into the jejunum and ileum its transport was equally delayed. They were able to demonstrate such an effect in a person with a profuse diarrhea, and since then I have successfully employed this drug clinically in some such cases.

In an application of this method of study to pitressin Elsom, Glenn and Drossner (25) found that the nausea and epigastric distress, which sometimes immediately follow its administration, are coincident with transient duodenal spasm, in spite of the fact that the predominant action in the duodenum is one of relaxation. The principle action of this drug, however, was found to be an increase of motility in the ileum and colon, in each of which periods of spasm alternated with periods of relaxation. Furthermore, they demonstrated a reciprocal action in that when the colon relaxed the ileum contracted and

vice versa. As the colon contracted its calibre was so narrowed that all haustral markings disappeared, air was expressed from the balloon and the barium mixture advanced rapidly.

INTESTINAL OBSTRUCTION

Finally I wish to refer to certain physiological observations made in connection with the therapeutic use of the apparatus in patients with intestinal obstruction. Wangensteen (26) had previously demonstrated the effectiveness of gastric and duodenal suction in obstruction, and had shown that a tube introduced into the stomach often slips into the duodenum within a few hours. As a result of experience with the Wangensteen technique and of observation of its beneficial results Johnston suggested to Abbott that they try to secure deeper penetration of the bowel in such cases by means of the double-lumened apparatus. In their first case the procedure was highly successful and led to their report (27) in 1938 of an experience in sixteen cases. Since then the method has been successfully applied in various surgical clinics, and I assume that those of you who are surgeons are more familiar than I am with the technique, its indications and contraindications and its effect on the mortality. I shall therefore refer only to certain aspects of our experience in the further development and use of the method that have a bearing on the physiology of the small bowel and on its possible value in diagnosis.

In the first place one is often asked how the apparatus can be passed downward through the intestine in the presence of a reversal of flow of the contents, such as is demonstrated by the success of the Wangensteen technique and by fecal vomiting. The answer to this question was given in 1867 by Brinton (28), who compared the mechanism to that of a syringe closed at its distal end and with a perforated piston. Any contained fluid in such a syringe is forced downward by the insertion of the piston, but on reaching the distal and obstructed end it is regurgitated backward through the opening in the piston. In support of his hypothesis he found that after the administration of castor oil to a dog with an intestinal obstruction the medication reached the area of the obstruction in spite of vomiting. Furthermore, we are not aware that orad peristaltic waves have ever been observed in the small intestine of man below the duodenum; certainly we have not seen them in many hundreds of intubations under the fluoroscope. We believe, therefore, that a reversal of motility does not imply a reversal of peristalsis, and the apparatus, by having its aspirating apertures distal to the balloon, provides a means for obviating a backward displacement of the apparatus by the regurgitating content of the bowel.

Next it may be asked what happens when the obstruction reaches the paralytic stage with no peristalsis. Any variety of obstruction, whether toxic, reflex or mechanical, may eventually lead to such stretching and relaxation

of the bowel wall that peristalsis ceases, but until the circulation is so restricted as to produce necrosis no paralysis in the sense of a potential loss of motor activity develops. Such pseudoparalysis disappears as soon as the distension is relieved by the aspiration of some of the bowel content, and then aboral peristalsis is resumed. Ingelfinger and Abbott (29) clarified this problem by their study of continuous kymographic tracings with simultaneous fluoroscopic observations in a series of 64 subjects. They found not only a fixed pattern of segmental and peristaltic waves and of motility for the entire tract of the normal subject, but a definite pattern indicative of obstruction. In the latter as the point of obstruction is approached the tonus of the bowel wall becomes more and more reduced and at the same time, because of the increase in calibre of the lumen in diastole, the peristaltic waves become larger and the motility more rapid. Finally, all muscular activity ceases, and then the motility depends solely on such waves as are present at a higher level or on variations in intraluminal pressure. The balloon, however, does not reach such an area of motor inactivity because before it gets to that point the distension is sufficiently relieved to permit a resurgence of the active, fighting and onrushing waves.

The chief merit of the two lumened apparatus lies in the fact that it reaches the point of obstruction and so acts as an internal enterostomy, or, in the case of an adynamic ileus, as a deflator of the entire bowel. Wangensteen himself admits that his technique has two disadvantages: that the tube does not reach the site of the lesion and that it does not permit use of the bowel above the lesion for purposes of nutrition. Both objections are overcome by intestinal intubation. Once the balloon reaches the upper jejunum the patient may be given fluids and glucose by mouth and, when it goes farther distad, any food may be run in that has a residue capable of being removed by the aspirating lumen. Thus the method makes available for the maintenance of the patient's nutrition all of the intestine above the balloon. This is of particular importance in cases of longstanding general peritonitis. Furthermore, since the tube decompresses the entire intestine above the lesion it gives a completely collapsed bowel, one that makes subsequent operation, if that is necessary, more simple. Finally, intubation of the intestine permits a reasonably accurate estimate of the fluid and electrolyte loss to the body (the latter equalling about 0.5 per cent of the total fluid output through the tube). Thus, without waiting for blood studies, which anyway may be inaccurate because of hemoconcentration, one knows approximately how much fluid and how much chloride should be administered intravenously to maintain an equilibrium.

In addition to its principal actions in decompressing the distended intestine, in aiding in the correction of fluid and electrolyte imbalance, in converting emergency cases of obstruction to an elective surgical status and in rendering subsequent operation less hazardous, intestinal intubation also may be an aid

in diagnosis. Not infrequently it is capable of localizing the site of an obstructive lesion and, by permitting the injection of a thin barium mixture at that point, of giving information as to its nature. In some instances the balloon may be arrested at a fixed point, even when ordinary roentgen ray studies are negative. In some such cases of ours the patient has eventually come to operation and always we have found a lesion, though at times it has not involved the bowel wall. Boon (30) found in one instance tubercles covering the peritoneal surface, in others some affection of the adjacent mesentery—a mesenteritis or a mesenteric adenitis. More often, however, we have found that when the balloon is arrested in the absence of the usual signs of obstruction the local injection of barium indicates some intrinsic bowel lesion, such as a kink or a regional ileitis. Anyway in those cases in which one would hesitate to give an ordinary barium meal a small injection of a thin mixture of barium into the area through the tube just above the lesion is not only safe but informative. Of equal importance is it that in cases in which the roentgenological study is negative or questionable ready passage of the balloon eliminates the presence of a significant organic lesion.

SUMMARY

In thus outlining briefly some of the results of investigations made in our clinic by means of small intestinal intubation I have omitted special reference to its dramatic effects in the management of obstruction. Instead I have thought it worthwhile at this time to emphasize its value in the study of nutritional problems, of drug effects and of the pathological physiology of the intestine. Also I have suggested its possible value in clinical diagnosis. In all of these fields, especially in that of the digestion and absorption of food factors in health and disease, further investigation is urgently needed. I hope that in the solution of the various problems that are presented the technique that we have described or modifications of it may prove useful.

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CONSTITUTIONAL HEPATIC DYSFUNCTION: CLINICAL STUDY OF THIRTY-FIVE CASES

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INTRODUCTION

Constitutional hepatic dysfunction deserves further discussion, not because of its effect on the health of the individual but because confusion with hemolytic disease, disease of the biliary tract and disease of the liver leads to unnecessary restrictions on activities of the patient and unnecessary surgical and medical procedures. The sole manifestation of the condition appears to be mild or latent jaundice. The essential pathologic finding is increased concentration of bilirubin in the serum, giving an indirect van den Bergh reaction. The jaundice may begin at any age and may be chronic or intermittent. It may be familial but is not always so. Constitutional hepatic dysfunction apparently does not produce symptoms other than the jaundice nor does it affect the health of the individual. Hemolytic and hepatic diseases do not cause the jaundice and, as the name implies, the jaundice is due to an inborn deficiency of the hepatic cells, chiefly with regard to their function of excreting bilirubin. It is a pure retention jaundice or, to state it another way, there is an abnormally high threshold for excretion of bilirubin. It is an acholuric jaundice. The terms "simple familial cholemia," "simple chronic icterus," "familial cholemia" (6–9, 15) and "familial nonhemolytic jaundice" (4) have been applied to the condition but we prefer the term "constitutional hepatic dysfunction" because the term indicates the constitutional nature of the condition as well as the organ now believed to be responsible.

Gilbert and associates (6–9) probably deserve credit for noticing the condition we refer to as "constitutional hepatic dysfunction." In 1902, they called attention to a group of individuals, in whose blood serum bile pigment existed in concentrations above normal and whose skin and scleras were often tinged yellow. To this acholuric jaundice they applied the term "simple familial cholemia" and "simple chronic icterus." While it seems likely that they included among their patients those with disease of the liver, chronic hemolytic icterus and even carotinemia, they seem to have recognized the existence of a familial type of jaundice unassociated with enlargement of the liver and spleen, and unassociated with bilirubin in the urine, corresponding to the condition we now prefer to refer to as "constitutional hepatic dysfunction."

With the development of the van den Bergh reaction, it was recognized that the bilirubin which produced the jaundice was of the same type as that seen in the serum of normal persons. Writers paid little attention to the condition in the next three decades but most of those who recognized it thought it due to constitutional inadequacy of the hepatic parenchymal cell. In 1935, Rozendaal, Comfort and Snell (13) and Comfort (2) alone, reported a series of sixty cases of slight or latent jaundice conforming to the definition of the condition. The occurrence of these sixty cases in a period of two years served to emphasize the relative frequency of jaundice of this kind. Meulengracht in 1939, Dameshek and Singer in 1941 and Curry, Greenwalt and Tat in 1942, discussed the condition and reported cases. Most interesting is the recognition of a similar type of jaundice in a certain strain of rats by Malloy and Lowenstein.

In the eight years since Rozendaal, Comfort and Snell reported their cases, the diagnosis of constitutional hepatic dysfunction has been made only thirty-five times at the Mayo Clinic. This by no means approximates the actual incidence of the condition. It seems certain that many other cases might be found in the records of the clinic. To find them it would be necessary to examine all records of cases occurring during this period, in which the concentration of serum bilirubin giving an indirect reaction, was more than 2 mg. per 100 cc. (Thannhauser-Anderson technic). The true incidence of the disease at the clinic is probably much nearer the average of 30 per year found by Rozendaal, Comfort and Snell than is the average of four per year in the years 1935 to 1942 inclusive. The diagnosis is made infrequently because the clinician often turns his attention into more positive channels when hepatic and hemolytic disease have been excluded as causes of the acholuric jaundice and the benign character of the condition has been established. The condition would be detected more frequently if the concentration of serum bilirubin were determined whenever the patient complains of slight jaundice, sallowness or biliousness.

COMMENT ON THIRTY-FIVE CASES

The ages of the patients at the time of registration at the clinic ranged from sixteen to sixty-five years and thirty (86 per cent) of the thirty-five patients were males. The jaundice had been noted since childhood in some cases; later in life in others. In some cases the jaundice had appeared only a few weeks before the patients registered at the clinic. Only 50 per cent of the patients knew that they were jaundiced or gave a history of jaundice. The jaundice was intermittent or chronic. The familial tendency of the jaundice was definite in twenty of the thirty-five cases, it was denied in five cases; in the remaining ten cases the patient did not know or could not find out after his

return home whether other members of the family were jaundiced. The jaundice was characteristically brought on or aggravated by fatigue, nervousness, worry, premenstrual tension, migraine, vertigo and intoxication. It was also much worse after a bout of constipation or dyspepsia. Interestingly, anger made it more pronounced. One elderly gentleman noted that he was more jaundiced after his two bouts of renal colic.

The essential pathologic condition in these cases was an abnormal concentration of serum bilirubin giving the indirect van den Bergh reaction. In the selection of our cases, those with a concentration of bilirubin less than 2 mg. per 100 cc. were excluded (Thannhauser-Anderson technic), so that borderline or questionable cases would not enter the consideration. The values for serum bilirubin ranged up to 10.9 mg. per 100 cc. The van den Bergh reaction was indirect in thirty-four of the thirty-five cases. In the remaining case, the van den Bergh reaction was of the delayed direct variety when the concentration was great. Rozendaal, Comfort and Snell reported similar findings. Such delayed direct, and direct, van den Bergh reactions are encountered in cases of hemolytic icterus when the concentration of bilirubin is high. These seem to be false positive direct reactions because they are indirect when the new technic of Sepulveda and Osterberg is employed.

The sole physical finding in these cases was the slight icterus. An occasional case of acholuric jaundice, without evidence of hepatic or hemolytic disease, but in which splenomegaly is present is encountered but these cases have not been included in the present consideration because they may be atypical cases of hemolytic icterus.

An elevation in the concentration of bilirubin was the only positive laboratory test. Tests other than that for serum bilirubin gave uniformly negative results. Anemia was not noted in any of the thirty-five cases. Morphologic studies of the cellular elements of the blood did not disclose abnormalities in thirty-three of the thirty-five cases. In two cases there was a questionable slight tendency to microcytosis but not to spherical microcytosis. Reticulocyte counts were normal in the nine cases in which they were made. The fragility of the erythrocytes to hypotonic salt solution was normal in all of the twenty-eight cases in which the test was done. In short, all evidences of hemolytic disease were lacking.

The increased concentration of bilirubin is the only finding so far reported pointing to the role of the liver in this condition. Slowing of excretion of bilirubin by the liver is confirmed by the bilirubin excretion test of hepatic function (4). Other tests of hepatic function rarely have suggested disturbance. In this series, the bromsulfalein test of hepatic function did not disclose retention of dye in any of the twenty-eight cases in which the test was done. Rozendaal, Comfort and Snell found only a very slight and perhaps

questionable retention of dye in the rare case. The hippuric acid test of hepatic function gave a normal result in the two cases of this series in which it was done. The excretion of urobilinogen in feces for twenty-four hours is said to be normal or slightly decreased (4). It may be said that dysfunction of the liver in these cases pertains chiefly to the excretion of bilirubin.

Roentgenograms made by the Graham-Cole technic disclosed a gallbladder that functioned normally in twenty-eight of twenty-nine cases; in the remaining case it was poorly functioning and there was a history suggestive of gallbladder colic.

The following abstracts illustrate the typical features of the condition.

Case 1. A man aged eighteen years registered at the clinic on August 13, 1939. His only illness had been malaria one year previously. He complained of jaundice of three years' duration. He was always a trifle yellow but more distinctly so in spells lasting one to two days. An increase in the jaundice was always associated with fatigue. No other members of the family were similarly affected.

Physical examination disclosed only a slight icteric tinge to the scleras; the liver and spleen were not palpable. Results of urinalysis and the routine serologic test for syphilis were negative. The concentration of hemoglobin was 17.3 grams per 100 cc.; erythrocytes numbered 5,540,000 and leukocytes 10,900 per cubic millimeter of blood. Morphologic studies of the cellular elements of the blood did not disclose any diagnostic findings. Roentgenologic examination of the thorax gave a negative result. Bromsulfalein test of hepatic function did not reveal retention of dye. The concentrations of bilirubin in the serum were 2.6 and 3.2 mg. per 100 cc. The van den Bergh reaction was indirect. Fragility of the erythrocytes to hypotonic salt solution was normal. The diagnosis was constitutional hepatic dysfunction.

The patient was dismissed after the nature of the jaundice had been explained. A letter was received from him May 7, 1943. He stated, "I seem to lack the endurance of a normal person. My eyes are always yellow but are helped by several days of rest. The icterus index varies from 25 to 44 units. I was called to the army in April, 1943, but was discharged after twelve days, eight of which were spent in the hospital for observation. I was advised to have an exploratory operation after my return to civil life."

Comment. Case 1 is a typical example of the nonfamilial, slight, chronic jaundice of constitutional hepatic dysfunction, noted first at the age of fifteen years. The patient was certain that his father, mother or brothers or sisters were not similarly affected. A history of previous hepatic disease and evidences of hepatic or hemolytic disease were lacking. An increase in fatigue accompanied the increased depth of jaundice, as is often the case.

Case 2. A man, sixty years of age, registered at the clinic in September, 1938. He stated that there had been recurrent episodes of jaundice for forty-five years. The episodes occurred every two to three years and lasted five to six weeks. These

were accompanied by exhaustion but not by pain, nausea, chills or fever. The last two episodes had followed attacks of renal colic. His only other illness in the past had been influenza in 1918. His mother, sister and niece experienced similar episodes of jaundice.

The only significant physical finding was a slight icteric tint to the scleras. Urinalysis, blood count and routine serologic test for syphilis gave negative results. Roentgenograms of the thorax, gallbladder, stomach, kidneys, ureters and urinary bladder were negative. Fragility of the erythrocytes to hypotonic saline solution was normal. Morphologic studies of the erythrocytes did not show features of hemolytic icterus. The hippuric acid test of hepatic function gave a normal result. The concentration of serum bilirubin was 3.0 mg. per 100 cc. and the van den Bergh reaction was indirect.

The patient stated in a recent letter that the yellowish tinge of the scleras had been noted two or three times a year since his dismissal. He had noted it when worried and tired and it seemed to be aggravated by nervous tension, anger or constipation.

Comment. Case 2 illustrates the familial occurrence of the jaundice and its not infrequent intermittent appearance. It also serves to emphasize the effect of fatigue and nervous factors in inducing the jaundice. That the concentration of serum bilirubin may be influenced by nervous stress has long been recognized (1, 5, 12) as has the existence of a so-called nervous icterus. Chrometzka has described jaundice following renal colic. Such spasmodic and emotional icterus has been ascribed to constitutional vagotonia with spasm of the common bile duct of vagal origin.

DIFFERENTIAL DIAGNOSIS

The elevations of concentration of bilirubin giving the indirect van den Bergh reaction found in constitutional hepatic dysfunction must be distinguished from those of hemolytic jaundice, particularly from chronic hemolytic jaundice, from those of chronic hepatic disease and from those persisting after acute hepatic disease. Further, they are distinguished from those of hemolytic disease by recognition of the hemolytic process and from that of chronic hemolytic icterus in particular by the absence of anemia, of abnormal erythrocytes and of splenomegaly. They are distinguished from those of hepatic disease by the history of, or the demonstration of, hepatic disease by appropriate physical and laboratory examinations.

The diagnosis is made only after the exclusion of hemolytic disease. In fact, the diagnosis implies that hemolytic disease is not responsible. However, in view of the following case in which hemolytic icterus, although somewhat atypical, developed in a case of constitutional hepatic dysfunction, a possible relationship between the two conditions must not be dismissed at this time.

Case 3. A man, aged thirty-three years, registered at the clinic in 1938. He complained of constipation. The scleras were slightly icteric. Physical examination

otherwise gave a negative result. Urinalysis, blood count, fragility test, examination of erythrocytes for morphologic appearance and bromsulfalein test of hepatic function gave negative results. The concentration of bilirubin in the serum was elevated (4.0 mg. per 100 cc.) and the van den Bergh reaction was indirect. The diagnosis was constitutional hepatic dysfunction. The patient had not been conscious of the jaundice and denied that members of his family were similarly affected.

The patient returned four years later, in 1942, because of the residue of Bell's palsy that had occurred seven months previously. The scleras were questionably icteric. The spleen was now palpable. There was no anemia, the erythrocytes were microcytic rather than normocytic but not spherical. Fragility of the erythrocytes was increased. The concentration of serum bilirubin was only 2 mg. per 100 cc. and the van den Bergh reaction was indirect. The diagnosis was acquired hemolytic icterus.

Comment.—It may well be asked how often features of hemolytic icterus will develop in cases of constitutional hepatic dysfunction and whether hepatic dysfunction of the type under discussion is a part of the picture of acquired or familial hemolytic icterus. It will be noted that in two of our thirty-five cases the hematologists found a tendency to microcytosis. Future developments in these two cases will be watched with special interest.

PROGNOSIS

The prognosis is excellent. It is true that many patients complain of functional disturbance, as has been pointed out, among others, by Rozendaal, Comfort and Snell. Meulengracht mentioned "the extraordinary monotony of fatigue and asthenia." Constitutional hepatic dysfunction is, however, compatible with good health. Some patients with the condition complain only of jaundice and appear to have very good endurance and vitality. We are not convinced that the fatigue and asthenia of such patients is due to the hepatic dysfunction.

The condition has not, so far as our records show, predisposed to development of cirrhosis. The case reported by Curry, Greenwalt and Tat is interesting in this respect. Biopsy was made of the liver of an Irishman, fifty years of age, who had jaundice of the type under discussion. His sister as well as he had been chronically jaundiced for many years. Splenectomy had been performed when the man was thirty-two years of age, without effect on the jaundice. Exploration when he was fifty years old revealed a normal gallbladder and a grossly normal liver. Biopsy disclosed normal hepatic structure and cells.

Rozendaal, Comfort and Snell found that cholecystic disease existed in 30 per cent of their sixty cases of constitutional *hepatic dysfunction. The possi*bility that gallstone disease develops more frequently among patients with con-

stitutional hepatic dysfunction than among normal individuals, as is true in cases of chronic hemolytic jaundice, was mentioned by these authors. This study does not give support to the possibility.

TREATMENT

Cholecystectomy, choledochostomy or splenectomy—one or more of these in a given case—have been employed in the treatment of the jaundice of constitutional hepatic dysfunction. It is not surprising that such procedures have not benefited the patients. Treatment on the basis of hepatitis or cirrhosis has been employed also with equally disappointing results. Actually, satisfactory treatment has not been devised and it is questionable that treatment is indicated if the condition does not affect the health of the individual, as we now believe it does not.

THE IMPORTANCE OF RECOGNIZING CONSTITUTIONAL HEPATIC DYSFUNCTION

While recognition of constitutional hepatic dysfunction apparently has little little importance so far as the health of the patient is concerned, its recognition is none the less important. If the jaundice is attributed to disease of the liver, a diagnosis of a disease carrying an entirely different and serious prognosis is fastened on the patient. If the jaundice is attributed to disease of the biliary tract, unnecessary cholecystectomy or choledochostomy will be, and has been, done. If the jaundice is confused with that of chronic hemolytic icterus, unnecessary splenectomy will be done without benefit to the patient. Finally, if the true importance of the condition is not recognized, unwarranted steps such as dismissal from the army or navy, or denial of insurance because of the jaundice, will be taken. In short, recognition of the condition has such a strong negative value to the patient that greater awareness of the entity than now exists is highly desirable on the part of the physician.

SUMMARY AND COMMENT

Thirty-five additional cases of constitutional hepatic dysfunction were reviewed from the records of the Mayo Clinic. Constitutional hepatic dysfunction may be acquired or congenital. As the name implies, the dysfunction is believed to be due to an inborn deficiency of the hepatic cell. Its sole clinical manifestation is slight icterus and the essential pathologic finding is increased concentration of serum bilirubin giving the indirect van den Bergh reaction, without bile pigment in the urine. It is apparently not due to hemolytic, biliary or hepatic disease. It apparently does not cause symptoms. Its recognition is important to the avoidance of unfavorable prognosis and unnecessary surgical treatment.

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DISEASES IN THE TROPICAL WAR ZONES

V. The Diseases of the Far East, Southwest and South Pacific

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INTRODUCTION

Three nosogeographic regions are included in this final chapter of the series because they are today so intimately related in the strategy of the Allied military commands. The first region includes Burma, Siam, Malaya, French Indo-China, China and Korea on the mainland of Asia, and the adjacent islands of Japan, Formosa, the Philippines, Borneo, Celebes, Sumatra and Java. This is the eastern portion of the Oriental Region and the adjacent eastern fringe of the Palearctic Region. The second region includes New Guinea, the Solomons, associated island groups and the northern (i.e. tropical) part of Australia and is referred to as the Australian Region. The third region includes certain parts of Micronesia, of which the Fiji and Samoan groups are of particular concern to us.

THE DISEASES OF THE AREA

This vast territory is afflicted with a large number of diseases which are present in native populations and to which our military forces have been or may be exposed. In countries such as China and Java, which are densely populated, hyperendemic and epidemic foci of disease constitute grave individual and public health problems.

The most prevalent and important diseases of the areas are malaria, many types of enteric infections, clonorchiasis, paragonimiasis, schistosomiasis, filariasis, kala-azar, plague, the typhus group of fevers, relapsing fever, leptospirosis, dengue, respiratory diseases, leprosy, smallpox, rabies, the venereal diseases, animal venenation and malnutrition.

Malaria. Malaria is endemic throughout practically the entire eastern Oriental and tropical Australian regions but is not established in the South Pacific (see fig. 32). Except for high elevations it is hyperendemic in Central and South China, Southeastern Asia, Formosa, the Philippines, Sumatra, Java, Borneo, New Guinea, and the Solomons. It is understandable that with a great variety of enviromnental conditions the epidemiology of the disease may differ considerably in different localities. The most important factors include climate, terrain and its relationship to fresh and brackish water, mosquito vectors, and density of population.

Since malaria is essentially a disease of warm climates, there are relatively few areas of high endemicity outside the tropics. The two most important exceptions in the Far East are the southern portion of Korea and the Yangtze Valley in China. Even in the tropics mountainous country, as in parts of Sumatra, Java, Borneo and New Guinea, are essentially malaria-free, but intermountain valleys at elevations of 2500 to 3500 feet in Yünnan Province China ("Burma Road") are highly malarious. Inland valleys, particularly where rice is cultivated on terraced hillsides; delta areas, with sluggish waters frequently coursing through extensive areas of irrigation canals; and low-lying coastal

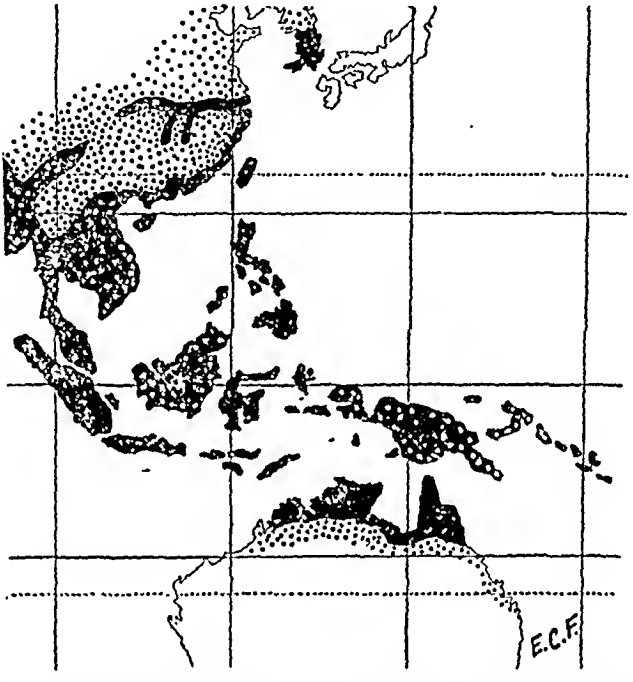

FIG. 32. Map of the Far East and the Southwest Pacific, showing the distribution of malaria. Areas of high endemicity are in solid black (25 to 75 deaths per 100,000 population); those with white dots on solid black indicate a rate of 75 or more deaths per 100,000; areas of light endemicity are stippled in black (original).

territory with multitudinous inlets of brackish water,—all these constitute breeding grounds for species of *Anopheles* mosquitoes which transmit malaria. Moreover, in each highly malarious area there is at least one *Anopheles* mosquito which is relatively domestic in its breeding and has a preference for human blood i.e. it is anthropophilous), thus providing an assured transfer of the malaria parasites. The more important vectors, together with their distribution and breeding habits in the areas under consideration are included in table 1.

As a rule, malaria is most prevalent in the Far East just before the summer monsoons and again in the late summer and early fall when mosquito breeding has been reestablished after the torrential rains. But in the tropical rainforest

belts of the Far East and Southwest Pacific hyperendemicity prevails essentially throughout the year wherever there is a human population sufficient to provide infection for the mosquitoes.

Ever since the Dutch, British and French established themselves in the Netherlands East Indies, in Malaya and French Indo-China, the foremost disease which confronted them was malaria. Until two decades ago Singapore was so malaria-ridden that it was difficult for white children to survive the third year. Moreover, the development of rubber, sugar cane, tobacco and rice on a

TABLE 1

The most important malaria-transmitting Anopheles in the Far East and tropical Australian regions

MOSQUITO	GEOGRAPHICAL DISTRIBUTION	BREEDING PLACES
A. aconitus	Dutch E. Indies (1,200–2,500 ft.)	Flooded rice fields, fish ponds, ditches
A. barbirostris	French Indo-China, Siam, Malaya, Dutch E. Indies	Shaded clear-water
var. *bancrofti*	New Guinea	Clear pools with vegetation
A. culicifacies	Burma, Siam, So. China (highlands)	Clear water
A. hyrcanus var. *sinensis*	China, Korea, Japan, French Indo-China, Malaya	Pools, canals, slow hill streams, swamps
var. *nigerrimus*	Dutch East Indies	Idem.
A. maculatus	Malaya, French Indo-China, Siam, S. China, Philippines, Dutch E. Indies, Borneo, Celebes, Flores Islands	Clear, sunny pools in fast streams
A. minimus	S. W. China, Burma, Siam, Malaya, Dutch E. Indies, Borneo, Sumatra	Grassy springs or streams, including moderately high elevations
A. punctulatus var. *moluccensis*	New Guinea, New Britain, Solomons, Moluccas, N. Australia	Pools, swamps, stagnant fresh and brackish water exposed to sun
var. *punctulatus*	Eastern part of Dutch E. Indies	Idem.
A. sundaicus	Siam, Malaya, Dutch E. Indies, Borneo, Celebes	Brackish water lagoons and pools
A. umbrosus	Malaya, Sumatra, Java, Borneo, Celebes, New Guinea, Solomons	Usually shaded pools and swamps

profitable commercial basis was seriously hindered by malaria. The Japanese faced the same difficulty in Formosa when they deprived China of this island in the 1890's and the United States encountered it in the Philippines following the Spanish-American War. Malaria has been largely responsible for the failure to colonize and develop Borneo, Celebes, Ceram and New Guinea on an extensive scale.

Although quartan malaria exists from Central China to Northern Australia, the prevailing types are falciparum (produced by *Plasmodium falciparum*) and

vivax (produced by *P. vivax*). The former type is responsible for the great majority of malaria deaths, especially as a result of cerebral complications. The latter is equally prevalent and constitutes a persistent underlying pathologic progress, with repeated relapses, sapping the energy of native populations and constituting a serious liability to Allied military personnel. Infection is readily acquired because of the large percentage of natives who constitute a continued source of infection for the mosquitoes, because of the relatively high percentage of infective-stage mosquitoes which repeatedly bite human beings, thus practically guaranteeing infection of human susceptibles, and because of the high degree of susceptibility as a result of an enervating climate and inadequate diet of native peoples.

Blackwater fever, a sequela of falciparum malaria, occurs sporadically throughout the malarious areas in both native and foreigh populations.

In highly malarious areas, even with modern anti-mosquito measures and available anti-malarial drugs, the malaria spleen rate frequently reaches 80 to 90 per cent, while the parasite rate in children may approach saturation. The annual mortality from the disease in such regions usually averages 2.5 to 5 per cent and during epidemics may reach 40 per cent.

In order to maintain effective labor in the plantations in Malaya and the Dutch East Indies, suppressive daily medication with quinine and atabrine has become a standard procedure.

Amebiasis. This disease is widely distributed throughout the area and in many parts is highly endemic (see fig. 33). As far north as Peking, China and Seoul, Korea 16 to 20 per cent of the native populations may be infected with *Endamoeba histolytica*, although frank amebic dysentery is relatively infrequent in these more temperate climates. As one proceeds down the China coast, and particularly as he reaches the more tropical region in French Indo-China, Malaya and the Philippines, the more dramatic manifestations of acute dysentery and amebic liver abscess commonly occur. Whether human excreta are used to fertilize growing garden crops, as in China, or the more fertile soil of the tropics requires no fertilizer to yield bountiful crops, the result is the same, namely, that insanitary disposal of human excreta is responsible for the propagation of the disease. In large urban centers like Hongkong, Manila, Saigon, Singapore and Batavia, a certain amount of sanitary sewage disposal has reduced the incidence or at least the clinical manifestations of the disease.

Twenty five years ago ipecac, emetin hydrochloride and emetin bismuth iodide were the anti-amebic drugs utilized by Western physicians in the Orient. Then the French preparation stovarsol partly supplanted these alkaloids, especially in Indo-China. Soon afterwards the German product yatren (iodoxyquinoline sulphonic acid) was introduced. It was so superior to the previously utilized drugs in the average clinical case of amebic colitis, and so much easier

for the patient to take, that it became the standard anti-amebic prescription several years before it received adequate clinical trial in the United States. Even in 1943 Japanese "yatrenine" was available and proved to be very satisfactory for cases of amebiasis among civilian prisoners of war in the Philippines.

Shigellosis and bacillary dysentry. Bacillary dysentery, the acute type of shigellosis, is widespread throughout the entire Orient and Southwest Pacific and has been reported from Micronesia. It is present in endemic form in native populations and is usually spread by person-to-person contact, less commonly through contaminated food, water supplies and flies. From time to time it breaks out in epidemic form. The death rate varies from 10 to 15 per cent or

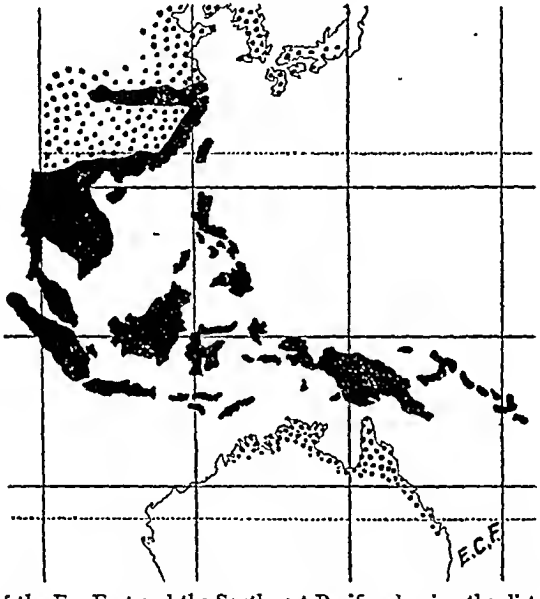

FIG. 33. Map of the Far East and the Southwest Pacific, showing the distribution of amebiasis. Areas of hyperendemicity are in solid black; those of lighter endemicity are stippled (original).

more of the cases bacteriologically diagnosed. Flexner is the prevailing type in all racial groups, Shiga second in Orientals and Sonne second among Occidentals, while Schmitz constitutes only a small fraction of the whole. In certain task forces of the Allied commands in the Southwest Pacific bacillary dysentery in acute form has constituted a temporarily serious problem. Sulfaguanidine has done much to relieve the acute symptoms and to speed recovery.

Typhoid and Paratyphoid Fevers. These infections occur throughout the entire area but are particularly prevalent in densely populated centers, especially where strictly native methods for the disposal of human excreta obtain. Food contamination, polluted water, flies and direct contact all contribute to the total morbidity but vital statistics are inadequate to provide a basis for visualizing

the control problem. Immunization has not been attempted on an appreciable scale among natives, partly because of the size of the task and partly because more urgent health problems have required the attention of the totally inadequate staffs of health workers.

Cholera. This disease is endemic in certain centers in Central and South China, French Indo-China and Malaya, and breaks out in epidemic form during the hot rainy season. In former decades it existed in the Dutch East Indies but has not been reported in Java in recent years, reportedly due to vaccinations initiated in 1926. However, in Celebes and nearby islands to the eastward, an epidemic due to el Tor organism broke out in 1937.

Cholera is rapidly propagated throughout endemic areas by cold drinks, sherberts, melons, other fruits and raw vegetables vended in the bazaars, all of which may become contaminated with the stools and vomitus of stricken individuals. Preliminary clinical reports suggest the high specificity of sulfaguanidine in the treatment of this disease. Nevertheless, eventual control must rest on the notification of all suspected cases and rigid sanitary disposal of human excreta.

Intestinal helminthiases. The helminths which parasitize the native populations of the Far East and the Pacific areas are almost legion and include hookworms, *Ascaris lumbricoides, Trichocephalus trichiurus, Strongyloides stercoralis,* several species of tapeworms, *Fasciolopsis buski, Metagonimus yokogawai* and related flukes, echinostome flukes, *Clonorchis sinensis, Paragonimus westermani, Schistosoma japonicum* and the filaria worms, *Wuchereria bancrofti* and *W. malayi.* All but the last five species are parasites of the digestive tract, while *Clonorchis* and *Paragonimus* infections are acquired from ingestion of infected foods. Schistosomiasis and the two types of filariasis develop after skin exposure.

Hookworm infection. This type of helminthiasis is extensively distributed throughout the entire area (see fig. 34). The etiologic agents are *Necator americanus, Ancylostoma duodenale* and *A. braziliense. Necator americanus* is almost strictly tropical in its distribution and is the predominant form, while *A. duodenale* is characteristically indigenous in the subtropics and adjacent part of the temperate zone north of the Tropic of Cancer. Nevertheless, for decades the migration of Chinese from their homeland to the south and southeast and more recently the Japanese occupation of mandated islands have introduced *A. duodenale* into the tropics of the Far East and warm areas of the Pacific, where this worm has become firmly established and constitutes about 10 per cent of the total hookworm picture. *A. braziliense* is known to occur in Formosa, the Philippines, Malaya and Sumatra, but is incidental from either a clinical or public health standpoint. It may manifest itself as an intestinal infection, but at times produces only a "creeping eruption", due to continued migration

of the infective-stage larvae through serpiginous tunnels in the deeper layers of the skin.

Throughout the tropics of the Far East and the Pacific regions as far eastward as Fiji hookworm infection is a real burden to the native peoples and in a high percentage of cases constitutes a grave disease entity. This is due in part to the toxic by-products of the worms absorbed into the patient's body but to a greater degree results from the blood sucked out of the intestinal wall by the worms. It is not uncommon for the hookworm burden in the Philippines, Malaya, or the Dutch East Indies to average as many as 500 or more per patient from late childhood through adult years. Since the infective-stage larvae de-

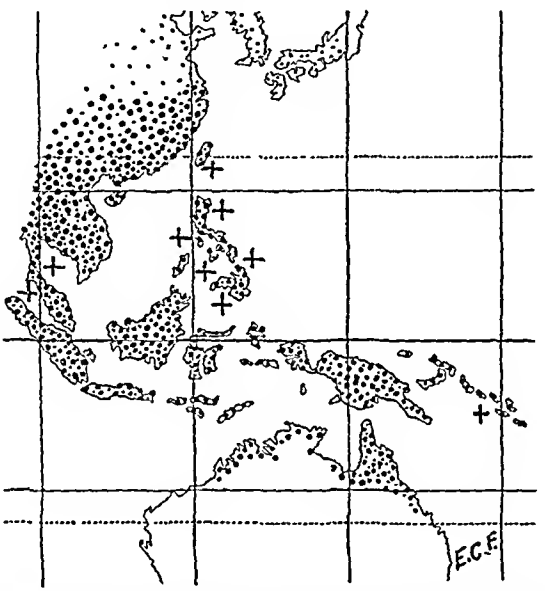

FIG. 34. Map of the Far East and the Southwest Pacific, showing the distribution of hookworm infection. The fine stippling indicates the distribution of *Ancylostoma duodenale*; the coarse stippling, *Necator americanus*. The + indicates a focus of *Ancylostoma braziliense* (original).

velop from eggs deposited in human feces on the soil, and since exposure commonly results from stepping barefooted on the polluted ground, the problem of control resolves itself into mass anthelmintic medication together with safe disposal of human excreta. This conclusion was reached by Darling and his associates a quarter of a century ago as a result of extensive field studies in these areas. Much work along these lines has been carried out, yet hookworm remains today a serious clinical and public health problem.

Ascariasis. *Ascaris lumbricoides* is, if anything, even more widespread than is hookworm throughout the Orient and tropical Pacific islands but its victims are conspicuously the younger children, in whom it constitutes a barrier to good

health. Mass treatment yields unsatisfactory results among the ignorant, frequently indigent peoples who do not understand the need for teaching their children not to pollute the ground with their feces.

Whipworm infection. *Trichocephalus trichiurus* is prevalent throughout the moist warm climates of the area. Like the hookworm, moisture is required for its development on the soil; like *Ascaris*, exposure results from ingesting fully embryonated eggs. Usually the worm burden must be high before marked clinical evidence of the infection appears. Although its epidemiology is fairly well understood, attempts at control have not been particularly successful.

Strongyloidiasis. Infection with *Strongyloides stercoralis* was first observed in Cochin China in 1876. Today the infection occurs in low incidence in China, but it is an important cause of disease in Formosa, the Philippines, French Indo-China, Malaya and the Dutch East Indies.

Trichinosis. As in other tropical areas trichinosis is practically unknown in the Oriental-Pacific regions.

Tapeworm infections. In Northern China and Japan, as in Southern Australia and New Zealand, hydatid disease, due to *Echinococcus granulosus*, is frequently encountered, but in the tropical intermediate territory it is recorded only for Tonkin (Northern Indo-China) and the Philippines. Beef tapeworm infection, caused by *Taenia saginata*, is widely distributed but occurs for the most part in Occidentals, occasionally in the Chinese, rarely, if ever, in other indigenous peoples. Pork tapeworm infection, produced by *T. solium*, is uncommon in the tropical zones, probably as a result of the thorough cooking of hog flesh by native peoples. In contrast, a larval tapeworm infection known as sparganosis, caused by the sparganum (i.e. larval stage of *Diphyllobothrium mansoni*), produces a human infection in South China, French Indo-China where it is frequently encountered as an ocular infection, and in the Dutch East Indies. The dog tapeworm (*Dipylidium caninum*) and certain rare (i.e. incidental) tapeworms of man have been occasionally described from the areas.

Fasciolopsiasis. This infection is produced by *Fasciolopsis buski*, a relatively large, fleshy trematode which lives in the duodenum of man and hogs. It is a common human parasite in Central and South China, Formosa, French Indo-China, Siam, Malaya, Sumatra and Burma. The infection results from ingesting the encysted larval stage attached to the "skin" of the water chestnut or the husk of the buffalo nut. Heavy infection produces indigestion and profound systemic toxemia.

Echinostome infections. Several species of echinostome trematodes have been described as endemic in the Far East, Malaya and the Dutch East Indies. These are acquired from eating raw snails or limpets (*Echinostoma ilocanum*, *E. revolutum*, *E. lindoensis*) or raw fish (*E. malayanum*).

Heterophyoid fluke infection. Many species of heterophyoid flukes have been

described from the Far East, of which *Metagonimus yokogawai* is the best known. All are very small worms, ovoidal or ovoid-elongated in shape, which are attached to, or are buried in the mucosa of the small intestine. They are acquired from eating raw fish, usually fresh-water species. Infection with these trematodes is common in Japan, Korea, Formosa and the Philippines, less frequent in China and elsewhere. The infection usually produces only a catarrhal inflammation of the intestinal epithelium, but in the Philippines Candido M. Africa and his associates have found that the minute eggs layed by these worms may filter into mesenteric lymphatics or venules and be carried to the myocardium, where they produce a syndrome simulating wet beriberi, or become lodged in the central nervous system, where they cause loss of motor or sensory function.

Clonorchiasis. This infection is produced by the Chinese liver fluke, *Clonorchis sinensis*, and extends from Japan and Korea through China into French Indo-China. It is also frequently encountered in Chinese residents throughout Malaya, the Southwest and South Pacific. In the tropical belt the areas of highest endemicity are in China, between Canton and Hongkong, and in the adjacent portion of French Indo-China, where 75 to 90 per cent of the native population may be effected. The disease results from eating raw or inadequately processed fresh-water fish. The mature worms live in the distal bile passages, where they provoke an extensive proliferation of the biliary epithelium and a fibrous encapsulation of the ducts, with symptoms of jaundice, cholecystitis or cholelithiasis. By pressure a periportal cirrhosis may result.

Paragonimiasis. Lung fluke infection, at times referred to as endemic hemoptysis, is widely distributed in the Far East and has been reported from the Southwest and South Pacific Islands. Although it is most frequent in Japan, Korea and Formosa, there are foci of infection in Central China, French Indo-China, the Philippines, Siam, Malaya, Sumatra, New Guinea and Samoa (the last named including American military personnel). The infection is commonly acquired from consuming the raw soft parts of infected crabs (or crayfish in Korea). The usual lesion is in the lungs near a bronchiole and produces paroxysms of coughing with hemoptysis. However, ectopic locations of the worms may cause peritoneal abscess, a Jacksonian type of epilepsy if the lodgment is in the brain or meninges, or abscess and fibrosis in the groin or neck.

Schistosomiasis. Although this infection was first recognized (1847) and described (1904) from Japan as a new disease produced by *Schistosoma japonicum*, it was soon found to have a vastly more extensive distribution in China. Today the endemic territory (fig. 35) is known to include five relatively small foci in Japan, three or four in the Philippines, one in Formosa, one near Lake Lindoë in central Celebes, essentially the entire equatorial third of China from the headwaters of the Yangtze River to the sea, coastal China from Shanghai

to Canton, and the valley of the Pearl River, with its north and west branches above Canton.

Schistosomiasis in the Orient, as in Tropical America, Africa, the Near East and Middle East, is produced by certain helminths (trematodes or "flukes") which live in venules draining visceral organs, hence the name "blood flukes". *Schistosoma japonicum* lives typically in the branches of the superior mesenteric vein and thus primarily affects the small bowel. Systemic toxemia caused by the by-products of the worms and their eggs and local reactions around the eggs of the worms infiltrated into perivascular tissues are responsible on the one hand for allergic reactions, inflammatory enlargement of the liver, dysentery

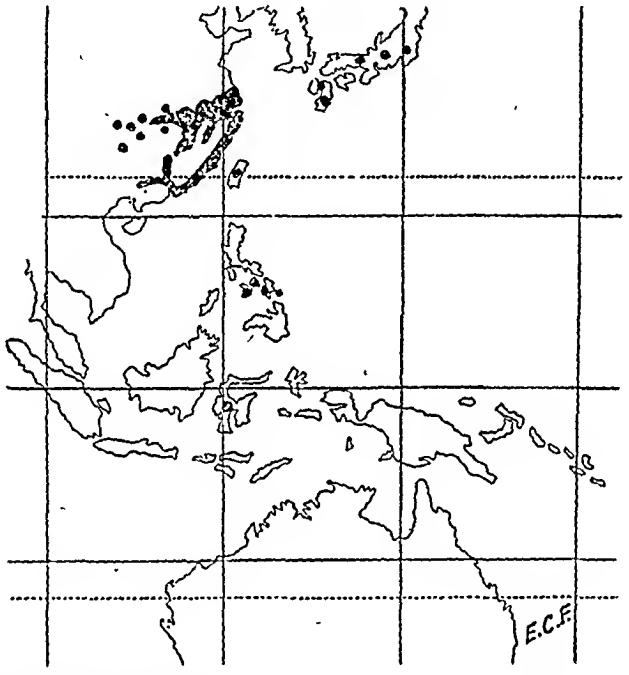

FIG. 35. Map of the Far East and the Southwest Pacific, showing in solid black the distribution of schistosomiasis japonica (original).

and fever, on the other hand for progressive fibrosis of the intestine. Moreover, because of the large number of eggs which pass into the portal vessel and filter out in periportal tissues, cirrhosis of the liver, with compensatory splenomegaly and with terminal ascites, characteristically ensues. If the number of worms in the mesenteric venules is considerable the disease may develop rapidly and death may occur within a year. Usually, however, the disease process is somewhat slower and is built up yearly by repeated exposure. The worms are known to have survived up to twenty five years in lightly infected individuals who have emigrated from endemic foci. Antimony therapy is specific.

Schistosomiasis occurs endemically only in areas where there are particular

species of snails which are the required intermediate hosts. Schistosomiasis japonica utilizes a small, turreted snail which lives among the weeds and grass at the edge of slowly moving or quiet, fresh water, or in rice nursery beds, but it readily survives several months of drying. The infective stage for man is the fork-tailed larva (cercaria) which emerges from the snail, becomes attached to the skin of man as he wades in the "infected water," and penetrates into the skin as the water drains off.

In China more than 100,000,000 people live in endemic territory and several millions are infected. American civilians and navy personnel have in years past become infected from bathing or wading in the backwaters or tributaries of the Yangtze River. Unless meticulous care is taken by task forces in endemic areas, individual or mass infection may occur. No suspected water should be utilized for external or internal purposes until it has been boiled, adequately filtered, chemically sterilized or has stood for 48 hours or more in a snail-free tank. For permanent control sanitary disposal of human excreta is indicated.

Filariasis. Although autochthonous cases of infection with *Dracunculus medinensis* have been reported occasionally from the Dutch East Indies, filariasis (*sensu stricto*) in the eastern part of the Oriental, the Australian and Micronesian areas consists of infection with Bancroft's filaria (*Wuchereria bancrofti*) and the Malayan filaria (*W. malayi*). The former species is widely distributed (Fig. 36), including Shantung Province in North China, Central and South China, southern Korea and Formosa, French Indo-China, Siam, Malaya, Sumatra, Java, the Philippines, Borneo, Celebes, Ceram, New Guinea, New Britain, New Ireland, the Solomons, North and Northeastern Australia, the Carolines, Marianas, Marshalls, Gilberts, Samoan group, Fiji, Ellice and probably other islands of the South Pacific. *W. malayi* is known to occur in two small foci in Central China, in Tonkin (French Indo-China), in Sumatra, Java, Borneo, Celebes, Ceram and New Guinea.

In filariasis bancrofti and filariasis malayi the parent worms reside in lymphatic vessels or lymphoid tissues. The mature females deposit delicate snake-like embryos called microfilariae, which in the case of these species are "sheathed". The microfilariae migrate out of lymphatic vessels into the blood stream and circulate in peripheral blood. In the Oriental and Australian regions they appear in the peripheral vessels characteristically at night and are said to exhibit nocturnal periodicity, but in the Micronesian area *W. bancrofti* has non-periodic microfilariae (i.e. they circulate through the cutaneous blood vessels at all hours of the twenty four).

These types of filariasis require certain species of mosquitoes as intermediate hosts and transmitters. *W. bancrofti* utilizes domestic species of *Aedes*, *Culex* and *Anopheles*, while *W. malayi* utilizes *Anopheles* in some endemic regions, *Mansonioides* in others. The mosquitoes pick up the microfilariae in blood

meals from infected persons and after a developmental period (without multiplication), varying from ten days to six weeks, the infective-stage larvae of the filaria escape from the proboscis sheath of the mosquito when it next prepares to take blood, then actively penetrate human skin.

Early clinical manifestations may include urticaria and other allergic conditions; these may occur soon after exposure or subsequently. The first significant symptom is a painful lymphangitis, frequently lymphadenitis, in a lymphatic vessel retrograde to the site where immature or adult worms are temporarily or permanently lodged. These acute episodes usually recur from

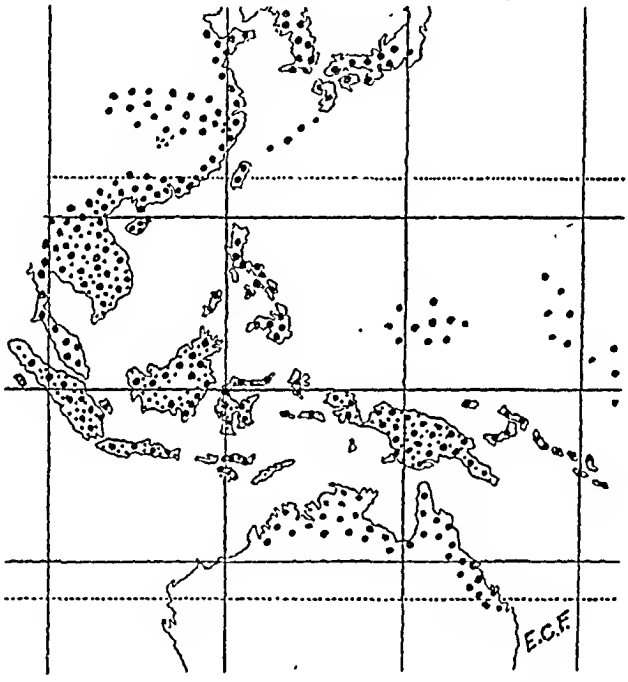

FIG. 36. Map of the Far East and the Southwest Pacific, showing the distribution of filariasis. The fine stippling indicates the endemic areas of *Wuchereria malayi*; the coarse stippling, *Wuchereria bancrofti* (original).

time to time, and the site of the inflammatory reaction may change if the worms are immature and are still migrating. In Bancroft's filariasis the lesions where parent worms are found are typically confined to the lymphatics of the lower trunk and lower extremities, especially in the groin and region of the spermatic duct. In the Malayan type, they are more likely to be situated in the upper trunk or axillae. But immature worms in Bancroft's type have been recovered all the way from the epitrochlear to the popliteal lymph nodes.

In native populations in endemic areas many cases of filariasis bancrofti or filariasis malayi exist in which adult females are producing microfilariae over a period of years without distinct symptoms. In such hosts lymphangitis and lymphadenitis are usually not distinctive features of the disease. Neverthe-

less, the host tissue reactions eventually strangulate the parent worms, which become moribund and die. The fibrotic process obstructs lymph flow, with resulting varicosities of the involved lymphatic vessels and frequently elephantiasis of the member.

White persons who are exposed in endemic areas usually exhibit more definite acute symptoms than natives do, but in years past the disease has usually manifested itself only after several years of exposure. Within the past two years American military forces in the Samoan foci of hyperendemicity have been repeatedly exposed to heavy inoculations of Bancroft's filariae. A considerable number have acquired the infection and have been hospitalized because of the acute involvement of lymphatic vessels which has most frequently localized in the vicinity of the spermatic duct. After the acute attack has subsided the patient feels entirely fit but in most cases a return to strenuous physical activity causes relapse. Up to the time this chapter was written none of the patients has exhibited microfilariae in circulating blood.

There is no eminently satisfactory chemotherapy in filarial infection, and operative procedures in the chronic cases leaves much to be hoped for. Thus, the one remedial measure which remains consists in elimination of domestic mosquitoes. This is a gigantic but not impractical task.

Kala-azar. Visceral leishmaniasis which is produced by *Leishmania donovani*, is confined to China and Manchuria (fig. 37). It is widely endemic in the north, northeast and northwest of China, but one focus of infection has been described for Kwangtung Province in the extreme south of China. Most of the patients are young children but adults are occasionally infected. In North China the disease is somewhat more serious than in India, but is less severe than in the Sudan. In Peiping the dog is a common reservoir of the infection, with cutaneous lesions. Kala-azar is amenable to antimony treatment, particularly neostibosan. Transmission occurs from bites of the sandfly, *Phlebotomus sergenti* and *P. sergenti* var. *chinensis*, during the summer and early fall. No effective control measures have yet been instituted.

Cutaneous and muco-cutaneous types of leishmaniasis do not occur in the Far East, Australian or Micronesian region.

Plague. There are several foci of endemic plague in the areas under consideration (fig. 38), including Inner Mongolia, Manchuria and the northeastern provinces of China, Anhwei Province up the Yangtze River from Shanghai, Fukien Province, Kwangtung Province with the adjacent island of Hainan, Yünnan Province in southwestern China (at least in previous decades), much of Cochin China, Cambodia, and Java. From these endemic centers the disease breaks out in epidemic form from time to time and in previous centuries, including the last decade of the 1800's, was spread pandemically by land and sea throughout much of the world.

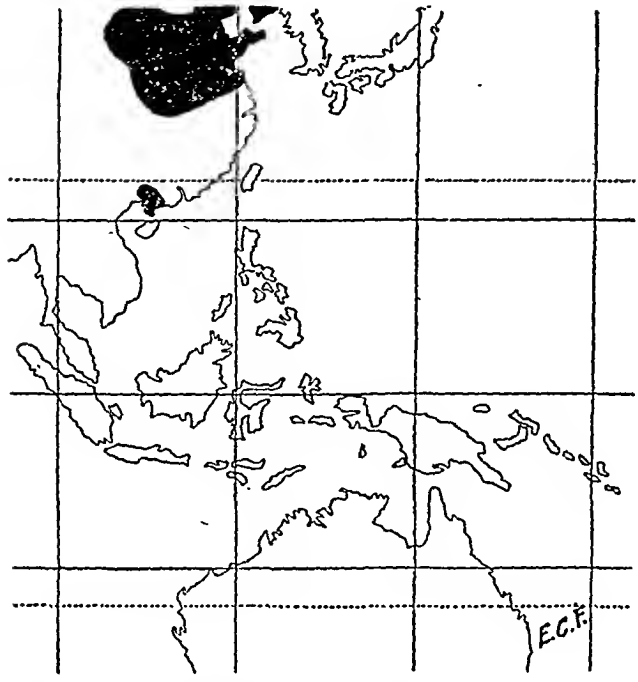

FIG. 37. Map of the Far East and the Southwest Pacific, showing in solid black the distribution of *Leishmania donovani*, producing visceral leishmaniasis (original).

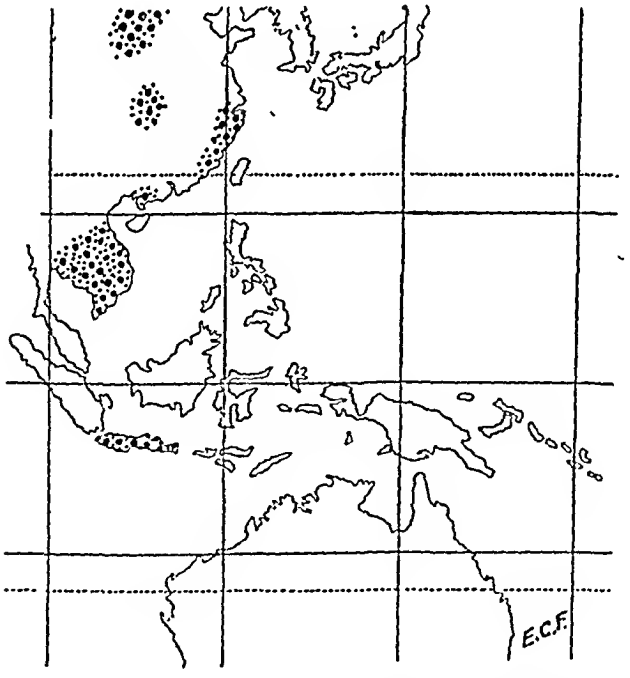

FIG. 38. Map of the Far East and the Southwest Pacific, showing the distribution of plague The coarse stippling indicates the foci of human plague; the fine stippling, enzoötic plague in rodents.

Transmission of plague and its epidemic outbreak are dependent primarily on two factors, namely (1) an endemic, relatively quiescent focus of the disease in rats or man and (2) conditions of temperature and humidity favoring the breeding of the tropical rat flea, *Xenopsylla cheopis*. Optimal conditions vary in different endemic foci. In Inner Mongolia and Manchuria the epidemic season may begin as early as July and continue to the end of the year. In South China it is more predominantly a vernal epidemic. In Indo-China it is spread throughout the first three quarters of the year. In Java, as a result of a relatively constant temperature throughout the year, epidemics may occur at any time but are more pronounced in the early fall following the monsoons.

For more than twenty years plague has not been a serious disease in North China and Manchuria, due to measures instituted by the Manchurian Plague Commission to set up quarantine barriers along the Mongolian border. Likewise, the number of cases reported from South China and Indo-China in recent years have been relatively small, at most only a few hundred per annum. In West China, with unsettled, congested conditions resulting from the Japanese invasion of Coastal China, many hundreds of cases have been observed yearly for the last few years. In Java most of the morbidity is confined to the western part of the island, where meteorological conditions and mountainous terrain favor the disease. Until recently the cases reported from Java have numbered several thousand a year.

The disease is usually bubonic in character, although the pneumonic type was prevalent during the epidemic outbreaks in Manchuria in past years. In Java plague has been greatly diminished since 1937, apparently due to extensive immunization with Otten's non-virulent living vaccine. In West China the use of sulfonamides has apparently been responsible for lowering the mortality when administered to patients during the early, strictly bubonic stage of the disease. No extensive anti-rat campaigns have been undertaken in any of the endemic foci.

The typhus group of fevers. Four epidemiologically distinct types of rickettsia infection are present in the Oriental-Pacific areas (fig. 39). Epidemic typhus occurs in Japan, Korea and North China, and is reported sporadically as far south as Northern Australia. Murine typhus extends from North China to Java. Scrub typhus has an extensive distribution, including Japan, Korea, Formosa, the Philippines, French Indo-China, Malaya, Sumatra, Borneo, New Guinea, New Britain, New Ireland (?) and northeastern Australia. Q fever occurs in Queensland, Australia. Each of these diseases will be considered briefly.

Epidemic typhus, which is transmitted by human body lice, is most prevalent in the northern countries of the Far East, where padded garments are worn

throughout the winter months. But the disease is apparently mildly endemic in the warmer areas, including Indo-China, Malaya, Sumatra and Northern Australia. (See Fig. 39). In these latter areas it is not always carefully differentiated from murine typhus and this confusion has resulted in heated controversy as to which disease is actually present. It seems reasonable to believe that when adequate study has been given to this question the situation may be found to be like that in Mexico, where not only epidemic and murine strains but also intermediate strains exist.

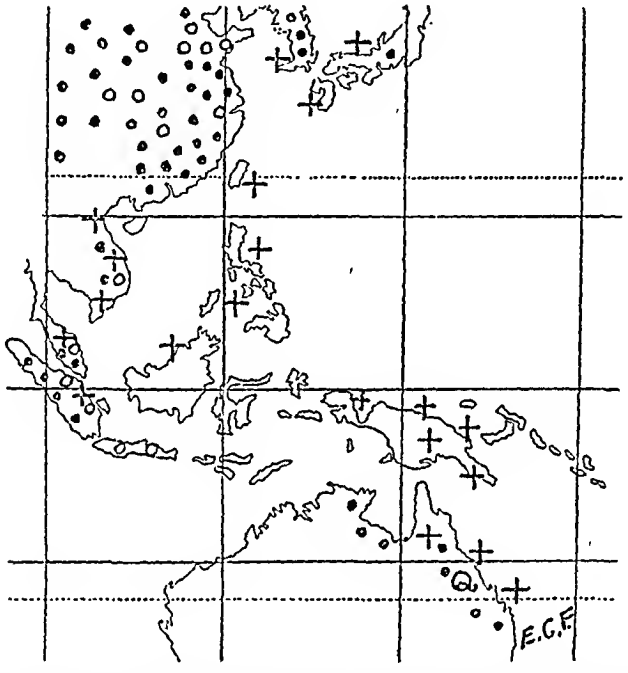

FIG. 39. Map of the Far East and the Southwest Pacific, showing the distribution of the typhus group of fevers. The coarse stippling indicates the foci of louse-borne epidemic foci; the small circles, endemic (murine) typhus; the +, scrub typhus (Japanese river fever); Q, "Q" fever (original).

Murine typhus, with the rat as reservoir and the rat flea as the transmitting agent, are now commonly recognized throughout the Far East (see fig. 39). The writer saw the first mild case of typhus fever in North China in 1925 in an American missionary. Previous to that time typhus contracted by Westerners in China had invariably been severe, although in natives it frequently took a milder course. In Malaya murine typhus is commonly referred to as "Shop typhus" because of its relationship to small mercantile establishments. This disease is undoubtedly more prevalent and more widely distributed than the meager present information indicates.

Scrub typhus (fig. 39), transmitted by red mites or chiggers, has been known to exist in Japan for several decades. In that country it is referred to as tsutsugamushi disease or kedani fever; in Formosa, as pseudotyphus; in Malaya

as scrub typhus, and in Australia as mite typhus or Mossman fever. In Japan it occurs only in the grassy vegetation bordering the coastal outlets of mountain streams, but in Formosa it extends into the mountains. In the nearby Pescadores Islands it is also present in dry, sandy terrain. In New Guinea it is found primarily in the tall kunai grass at the edge of the jungle.

Mites suck blood only during their larval stage and feed on plant juices in their nymphal and mature stages. The rickettsias of scrub typhus are congenitally transmitted from one larval stage to the next. Field mice, rats, the bandicoot, the bush pig and many species of birds are the normal hosts of these ectoparasites during their blood-sucking stage, but none of these needs be a host of the rickettsia because of its congenital transmission in the mite. Human beings who trail through the particular regions where the mites abound are liable to infestation by the mites, and acquire scrub typhus if the mites are infected. Because of protective clothing, shoes and socks worn by Allied troops in occupied endemic foci, mites are more likely to become attached to clothing and to suck blood from them than from the practically unclothed natives. This accounts for the greater likelihood of infection developing in newly arrived troops than in the indigenous population.

Scrub typhus is usually characterized by a black eschar at the site where the mite feeds. Although the microscopic lesions in and around the smaller blood vessels are less distinctive than those of epidemic typhus or tick-transmitted spotted fever, the typhus-like symptoms may be severe. This disease is immunologically and serologically distinct from epidemic or murine typhus, spotted fever and Q fever. Sera of patients agglutinate Proteus OXK but not OX2 or OX19. The disease is now being studied in all of its aspects by American military and civilian physicians and epidemiologists.

Q fever is endemic in northern Queensland and possibly extends into the adjacent Northern Territory of Australia (see fig. 39). The etiologic agent is *Rickettsia burneti*. (*R. diaporica* of "nine-mile fever" in Montana is apparently identical). In Australia the organism is transmitted by the ticks, *Haemaphysalis humerosa* and *Rhipicephalus sanguineus*. The bandicoot is the common wild reservoir in the Australian bush but wild rodents, cattle and other mammals are susceptible. Man may acquire the infection in the bush but probably more commonly is exposed while in contact with cattle. Clinically Q fever has some of the characteristics of typhus fever, but the rash is absent, the leukocyte count is essentially normal and pulmonary symptoms simulating an atypical pneumonia may occur. Agglutination of Proteus organisms does not take place in the presence of patient's serum, but suspensions of *R. burneti* (1:10) prepared from mouse spleen are agglutinated. Control may be effected by avoiding tick infestation in edemic areas.

Relapsing fever. This infection is endemic throughout the Maritime Provinces of the U. S. S. R., Manchuria, Korea, the western part of the main island of Japan, and from the Greal Wall of China to the southern part of French Indo-China. It is not known to be indigenous elsewhere in the regions herein considered. The spirochete which is the etiologic agent of the disease is louse-transmitted. As a result the infection develops to epidemic proportions during winter's cold, famine and floods, or wherever human beings in distress are herded together.

Leptospirosis. This group of closely related clinical entities has a very extensive distribution throughout the Far East and the Australian area. The etiologic agents belong to the genus *Leptospira.* The classical member of the group is *L. icterohemorrhagiae*, which was first described by Inada, in 1915, as the causative organism of infectious jaundice, more commonly known as Weil's disease. One or more species of *Leptospira* are known to be present in man or reservoir hosts in Japan, Formosa, North China, French Indo-China, Malaya, Sumatra, Java, Celebes, Borneo, the smaller islands of the Dutch East Indies and northeastern Australia.

In addition to *L. icterohemorrhagiae* and *L. canicola* the following species are recognized from the Oriental and Australian regions: *L. akiyami* (Japan, Indo-China, Malaya, Sumatra, Java); *L. australis* A and B (Australia); *L. autumnalis* (Japan, Indo-China, Dutch East Indies); *L. bataviae* (Java, Borneo, Celebes); *L. hebdomadis* (Japan, Indo-China, Sumatra [rare]), *L. javanica* (field rats in Java); *L. pomona* (dogs and hogs, W. Java); *L. pyrogenes* (Malaya, Sumatra, Java); *L. eruthyan* and *L. nallathamby* (Malaya). The great majority of these strains are carried in brown rats, black rats, field rats or field mice, which contaminate water and earth with their urine containing the leptospiras. Persons working in occupations favoring contact with the excreta of these animals, as laborers in sewers, dairy employees, workers in abattoirs, cane cutters, workers in rice fields, gardeners, bargemen, dock workers, or those who drink or swim in "infected water," are most commonly infected.

Dengue and Yellow Fever. Dengue (fig. 40) is so widely distributed throughout the entire Orient from the Maritime Provinces of the U. S. S. R. to Malaya, throughout northern and Northeastern Australia, the Dutch East Indies and all the islands of the Southwest, South and Central Pacific, that it may be regarded as the most extensively endemic disease of the entire area. It even occurs in northern New Zealand. It is commonly transmitted by *Aedes aegypti*, but *A. albopictus* has been incriminated in China, Japan, the Philippines, Sumatra and in the recent epidemic in Hawaii, *Armigeres obturbans* in Formosa, and on epidemiologic grounds *Aedes scutellaris hebrideus*, with habits similar to *A. albopictus*, is believed to be the transmitter on Espiritu

Santo, New Hebrides. Newcomers, as American military forces, are non-immune and on exposure usually develop an illness which is prostrating and incapacitating for a week or more although it is not dangerous to life.

Yellow fever has not occurred in the area during historical times. The natives are all non-immune and require protection against its introduction from Africa or South America.

Respiratory diseases. The more important respiratory diseases are prevalent throughout the area. Pneumonia, especially lobar pneumonia, is more common and the mortality rate is higher in natives than in Westerners exposed to the same types of the infection. Influenza likewise has an extensive dis-

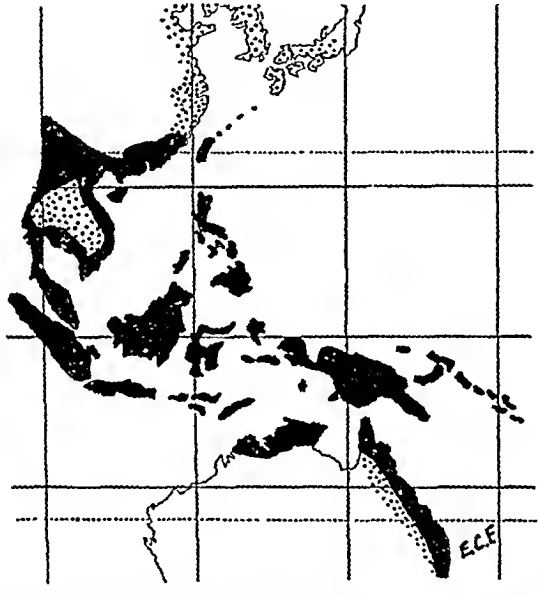

FIG. 40. Map of the Far East and the Southwest Pacific, showing the distribution of dengue. The areas of hyperendemicity are indicated in solid black; those of milder endemicity, by stippling (original).

tribution. In addition, bronchial spirochetosis is encountered fairly frequently from North China to the Dutch East Indies. Pulmonary tuberculosis is very common in native peoples. About 5 per cent of all hospital admissions in the Dutch East Indies have tuberculosis, and of these patients one in every five dies of the disease.

Leprosy. This disease is widely endemic throughout almost the entire Far East, Southwest and South Pacific regions (see fig. 41). The areas of moderately heavy infection (1 to 5 per 1,000 population) include Japan, Korea, three foci in central North China, practically all of Central and South China, French Indo-China, Malaya, and all of the islands to the south and southeast. North-

eastern Australia is only incidentally involved. In China alone there are an estimated one million lepers or about 2.5 per thousand population; in the Philippines, at least 20,000 or 1.5 per thousand. In the Dutch East Indies the disease is particularly prevalent in North Sumatra, Bali, the Moluccas, Celebes and New Guinea. It is more common in the Chinese and Indian populations than among natives. As in other regions of the world where leprosy is relatively common, the presence of the disease is correlated with poverty, crowding and poor sanitation.

Smallpox. In the Philippines, Straits Settlements and the Dutch East Indies extensive immunization has been underway for many years, with the result

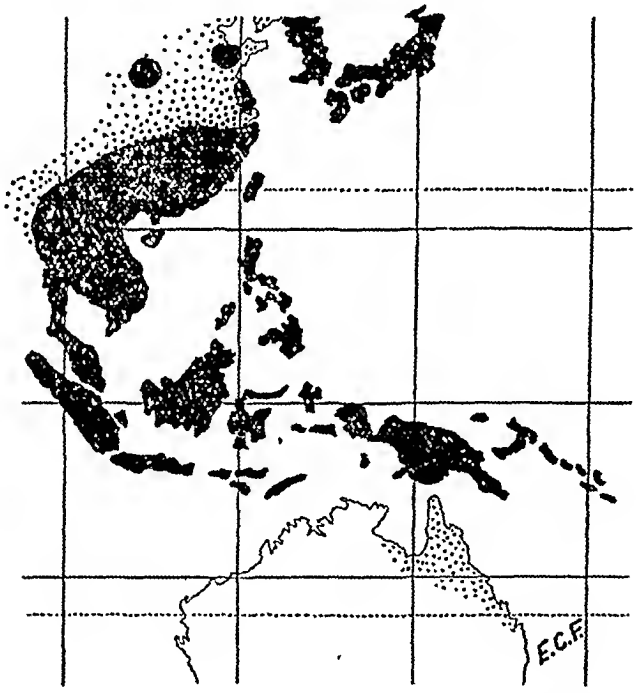

FIG. 41. Map of the Far East and the Southwest Pacific, showing the distribution of leprosy. Areas of moderately high incidence (i.e. 1 to 5 per cent) are indicated in solid black; those of lighter endemicity are stippled (original).

that smallpox epidemics are few and of small size. On the other hand more than five thousand cases were reported from French Indo-China in 1943. The disease was very common in pre-war times in China, Korea, Japan and Malaya.

Venereal diseases. From Tokyo and Mukden to Singapore and Batavia, brothels flourish by virtue of police protection, and as a result venereal diseases, particularly syphilis and gonococcus infection are widespread. Depending on the particular area, the estimated amount of these diseases ranges from 10 to 50 per cent of the population. Relatively few cases of the many millions who are infected utilize other than native remedies. Syphilis was not present in the Southwest and South Pacific islands until recent years and even today

is no serious problem. Granuloma venereum occurs in Korea, Formosa, China, parts of New Guinea, Borneo, Celebes, and the Solomons. Lymphogranuloma verereum has been reported from Korea, Formosa and is common in parts of New Guinea.

Yaws replaces syphilis among the native populations in many of the countries of the areas under discussion. It is not an important public health problem in China or Formosa, but in the Philippines and French Indo-China, in Malaya and in the Dutch East Indies the disease is common (at times affecting 10 to 20 per cent of certain population groups). Proceeding eastward through the Solomons to the islands of Micronesia, up to 75–90 per cent of the inhabitants suffer from yaws. In Java and other Dutch possessions intensive mass treatment with neosalvarsan has been under way for several years.

Other infectious and contagious diseases. The most widespread of these diseases not yet mentioned is trachoma. It is frequently encountered in China, Japan and wherever these peoples have immigrated in any numbers. Rabies is also a serious problem in countries where dogs roam about by the thousands, as in China. Tetanus and anthrax are common, especially in countries where human excreta are used for fertilizer. Australian "X disease" and other types of encephalomyelitis occur in several localities from Manchuria to Australia.

Dermatoses. Skin diseases of various etiologies abound in the Far East and Pacific areas. Of particular importance are scabies, pediculosis, the dermatomycoses, ulcus phagedenicum tropicum and pemphigus.

Venenating and poisonous animals. In addition to numerous arthropods (mosquitoes, biting midges, sandflies, fleas, lice, bedbugs, ticks and mites) which annoy man when they are not vectors of pathogenic microorganisms, certain arthropods, as scorpions, may at times introduce neurotoxic venoms which cause serious illness.

More important are the venomous snakes. On the mainland of Asia, in Formosa, the Philippines and the Dutch East Indies west of New Guinea the snakes are similar to those of India and Burma and include the arboreal bamboo viper (*Trimeresurus gramineus*) with a prehensile tail, the pit viper (*Agkistrodon rhodostoma*), the Indian cobra (*Naja naja*) and close relatives, the king cobra (*Naja hannah*), the common krait (*Bungarus candidus*), the banded krait (*B. fasciatus*) and the yellow beaded krait (*B. flaviceps*). In the Australian region the death adder (*Acanthophis antarcticus*) is particularly venomous. In the waters of the Southwest Pacific from Formosa to Australia and New Caledonia there are many species of sea snakes which have very potent neurotoxic venom, but seldom strike unless they are attacked.

There are several species of marine and fresh-water fishes in the Southwest, South and Central Pacific which possess poison glands opening at the base of

fin rays or barbs. When stepped on they frequently produce local pain and swelling, later necrosis at the site, at times lymphangitis and ascending motor paralysis. The barbs may also be contaminated with tetanus spores.

Certain fishes of the herring family which are abundant in the Pacific areas are poisonous when used as food.

Deficiency diseases. While rickets and osteomalacia, pellagra and sprue (especially among Westerners living under native conditions) are encountered in the Orient and Southwest Pacific, beriberi is the one deficiency disease which is prevalent throughout practically the entire tropical and subtropical portion of these regions. The peoples for the most part depend on rice as their main article of food, supplementing it wherever possible with fish. Polished rice is almost invariably preferred and provides the basis for the vitamin deficiency. Although public health officials in all of the countries concerned have attempted to educate the populations to substitute "brown rice" for "white rice" the results have not been particularly encouraging.

CONCLUDING REMARKS

In the series of four papers dealing with the infections of warm climates and involving six relatively distinct geographical areas, the writer has presented information about the autochthonous diseases encountered or likely to be encountered by American military forces who have been in training in the Tropics, those in tropical combat areas or in potential war zones. Since the first paper appeared in Gastroenterology (November 1943) some of the potential territory has been won but much remains to be conquered, particularly in the Orient and Southwest Pacific.

The information on diseases in many of these countries is fragmentary, but its presentation is justified in so far as it is authentic. In general, it may be stated that with few exceptions all of the cosmopolitan diseases are relatively prevalent in warm climates. Moreover, the diseases of the white man, to which the natives of many tropical countries were unexposed until recent decades, are particularly severe in native peoples. In addition, there are certain diseases in Africa, India, the Far East and the Australian region, which are predominantly tropical or Oriental, or are hyperendemic in these countries and seldom assume comparable importance in temperate climates, unless by ill chance they are introduced from the tropical mother countries of the disease. Plague, cholera, yellow fever and dengue are typical examples, while malaria, Bancroft's filariasis and amebiasis are possible competitors for this distinction.

The medical departments of the military forces have already encountered the majority of the clinical and public health problems presented in this survey. Even after the war has been won they will face the equally serious difficulties of medical and sanitary rehabilitation of the liberated peoples.

Meanwhile, civilian physicians in the United States will have in increasing numbers personnel discharged from the armed services. Many of these individuals will have been exposed to tropical diseases which will manifest themselves in relapse or in chronic form after return to civilian life. A consciousness of these possibilities on the part of the civilian physician will undoubtedly aid in accurate diagnosis, and treatment. In many cases it will shorten the period of semi-invalidism, and may prevent the actual establishment of some of these infections in the United States.

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A CRITICAL EVALUATION OF THE NEUTRAL RED EXCRETION AND ACID SECRETION TESTS OF GASTRIC FUNCTION IN THE NORMAL AND IN SUBJECTS WITH GASTRIC DISORDERS

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INTRODUCTION

Neutral red excretion was first used as a clinical test of gastric function by Glaessner and Wittgenstein (1). The rate of excretion of neutral red was regarded by several continental investigators to be an index of gastric acidity (1, 2, 3). However, it soon became clear from the work of Davidson et al. (4), Piersol et al. (5), Winkelstein (6), Zabilis (7) and Lourja and co-workers (8) that neutral red could be excreted in the presence of complete anacidity and that the rate of excretion of neutral red could not be used as an index of acidity. The neutral red test therefore fell into disuse.

For the last forty years the secretion of acid by the gastric mucosa has been employed to assess gastric function. Vanzant et al. (9), Alvarez (10), Polland (11), Klumpp and Bowie (12) and Ruffin and Dick (13) have demonstrated that, owing to the wide range of acid secretion in normal individuals, the diagnosis of gastric dysfunction, on the basis of acid curves, could never be considered reliable. The reports of wide fluctuations in acid secretion in the same normal individual on different occasions (13, 14, 15) raised another serious objection to the use of acid secretion as an indicator of the functional efficiency of the stomach.

For a time it was felt that the establishment of "histamine anacidity" at least, was indicative of gastric disorder. However, the occurrence of periods of "spontaneous histamine anacidity" in the same individual without any definite gastric disease (14), as well as the presence of spontaneous anacidity, even after histamine, in several cases who secreted free acid on other occasions (15), made it quite clear that anacidity even after histamine could not be used as a criterion of gastric dysfunction. Moreover, it has been shown recently that 20% of all patients with anacidity after the administration of histamine have apparently a normal mucosa as assessed gastroscopically (16). On the other hand, Pollard and Cooper (17) have reported that hypertrophic gastritis may be associated frequently with normal acidity.

The accumulated evidence to date indicates that with existing techniques, the information acquired from the study of the acid secreting powers of the stomach is unreliable in establishing the presence of disorders of the stomach.

The rejection of the neutral red test merely because it does not seem to bear

any relation to the acid curves is not justified. The studies of Lourja and associates (8), Olleros (18) and Gillman (19) have shown that the excretion of neutral red is not only unrelated to acid secretion, but indeed is an expression of a totally different function of the stomach from that concerned with acid secretion. The study of the capacity of the stomach to excrete substances may throw light on other little known aspects of normal and abnormal processes of the stomach mucosa. This is indicated by the work of Lourja (8), Olleros (18), Henning (20), Winkelstein (6), Katsch and Kalk (2) and Morrison (21) on the excretion of neutral red, and Martin (22) and Solovey (23) on urea excretion by the gastric mucosa.

The acid secretion test of gastric function has fallen into disfavour only after being in vogue for many years. The occurrence of such a long lag period between the first discription of the test and the recognition of its limitations can be ascribed mainly to the fact that the test was applied in the clinic as a diagnostic procedure before the range of acid secretion and the physiological fluctuations of the secretory activity of the stomach in normal subjects had been satisfactorily established.

Profiting by this experience, it was decided firstly to study the excretion of neutral red by the stomach in a sufficiently large number of "normal" individuals, and secondly, to examine the excretion of neutral red in the same subjects repeatedly over a period of months to determine the fluctuations which may occur even in the absence of gastric disease. Furthermore, the results obtained with the neutral red test in subjects with abnormal gastric function were compared, not with unreliable indicators, such as gastric acidity, but rather with other criteria of a clinical, biochemical and radiological character, as well as direct observation of the gastric mucosa at operation and autopsy.

One of the objects of the present paper will be to record those improvements in the performance of the neutral red test which have been developed as a result of its extensive use in our clinics. These improvements have been evolved in order to facilitate the expression of qualitative changes in such a quantitative fashion that the results can be examined statistically. Such a statistical approach to clinical problems is of paramount importance because it allows the results of investigators in different parts of the world to be compared.

The date used in this study have been arranged so that, firstly, the excretion of neutral red in so-called normal individuals can be examined and the physiological fluctuations in the same individual of acid secretion and dye excretion can be established. Thereafter, the results obtained in a selected series of cases where gastric dysfunction was known to exist will be presented in order to discover whether the neutral red test can be used diagnostically.

In the first part of this study, 90 individuals with apparently normal gastric function were examined once only, while 15 of these subjects were examined

several times at various intervals. In the clinical section of this investigation no less than 300 tests were conducted on patients with proven gastric disorders. Sixty-five cases have been selected to show how valuable the neutral red test can be, not only in establishing the existence of gastric dysfunction, but also in assessing the degree of damage and the response of the stomach to therapy.

METHODS

Soon after the intravenous injection of neutral red in a normal person, the dye appears in the stomach and stains the gastric juice pink. Within a variable period thereafter the gastric juice is stained deep red; later the intensity of staining diminishes, and when the dye is no longer excreted in the stomach, the juice again becomes colourless.

Since the dye is not only excreted, but also concentrated to a considerable degree by the gastric mucosa, it is possible to make four separate measurements of the ability of the stomach to excrete neutral red, thus:

1. The *excretion time* can be determined by measuring to the nearest minute with a stop watch, the time elapsing between the moment the dye is injected and the first macroscopically recognisable pink staining of the gastric juice.
2. The *degree of concentration* of neutral red by the stomach can be guaged by comparing the colour of each sample of gastric juice aspirated with standard dilutions of the dye.
3. The time taken for the dye to reach its maximum concentration in the gastric juice, i.e. the *concentration time*, can be measured.
4. The total quantity of neutral red excreted during a standard period of time can be estimated.

The ability of the gastric mucosa to excrete neutral red is estimated in this study by measuring the excretion and concentration times and the degree of concentration of the dye in the gastric juice. In order to obtain the various readings, the following routine procedure is adopted:—After a 12-hour fast the naso-pharynx and soft palate are anaesthetised by spraying with a 1% solution of "Decicain." A Levin duodenal tube, with a catheter tip, is then introduced into the stomach by the nasal route. The local anaesthesia facilitates intubation and prevents the gagging and discomfort usually associated with this procedure.

The resting juice is aspirated, and the stomach is then thoroughly washed with 100–150 cc. of tepid water in the manner previously described (19).

Patients are instructed to expectorate any saliva excreted during the period of the test.

Five cc. of a 1% sterile solution of neutral red are then injected intravenously, and a stop watch is started. Aspiration of the gastric juice is begun immediately, and is continued at minute-intervals for the first thirty minutes. The

excretion time is measured to the nearest minute with a stop watch. After the dye has appeared the gastric juice aspirated every minute is delivered into a separate test tube of $\frac{1}{2}$ inch diameter, and compared macroscopically with standard dilutions of neutral red in distilled water put up in test tubes of the same diameter. The following arbitrary scale is recommended for clinical purposes:

trace	1/300,000 aqueous soln. neutral red
1	1/200,000 aqueous soln. neutral red
2	1/100,000 aqueous soln. neutral red
3	1/75,000 aqueous soln. neutral red
4	1/50,000 aqueous soln. neutral red
5	1/30,000 aqueous soln. neutral red
6	1/20,000 aqueous soln. neutral red

The degree of concentration of neutral red in each specimen of gastric juice is recorded, as is also the time of aspiration of each sample. The time taken for maximal concentration to be attained, i.e. the concentration time is thus easily estimated.

When the flow of gastric juice is poor, 10 cc. of water are injected through the tube and immediately aspirated. This procedure is particularly valuable in ascertaining the presence of neutral red when excreted in very small quantities.

Since neutral red assumes a yellow colour in an alkaline medium, occasionally it may be mistaken by the inexperienced investigator for bile in alkaline gastric juice. To avoid this error, all yellow specimens of gastric juice are acidified with hydrochloric or glacial acetic acid, and if neutral red is present it turns red.

If neutral red is excreted and concentrated to a maximal intensity within 30 minutes, the stomach is considered to be normal and, for practical purposes the test is regarded as having been completed. Study of acid secretion in the presence of a normal dye excretion is superfluous. However, if the excretion of neutral red is abnormal, according to the criteria detailed below, or if both the dye excretion and acid secretion are being estimated simultaneously, then 30 minutes after neutral red has been administered, 0.5 mgm. of histamine acid phosphate is injected hypodermically, and aspiration of gastric juice is continued for a further 90 minutes.

It is important to mention here that the dose of neutral red employed for this test is non-toxic. Since the dye is excreted in the urine and faeces and colours these excretory products red, it may be mistaken for blood. Unnecessary inconvenience and anxiety is avoided by warning both the patient and the nursing staff that the urine and faeces may remain red for 10–12 hours.

In order to estimate the acid content of the gastric juice, mucus and neutral

red are removed by filtration through cotton wool in the manner previously described (19). Free and total acid are determined on a 5 cc. aliquot of each filtered specimen by titration with N/20 sodium hydroxide freshly prepared from a stock solution. Two drops of a mixture of Töpfer's reagent and phenolphthalein are used as the indicator. The presence of pepsin is determined by Mett's method.

Both the collection of specimens and the laboratory procedures in this investigation were conducted by the author. This eliminated those errors which may occur from the faulty collection of specimens by individuals not experienced in conducting the test; it also prevented those inaccuracies in the results which may have occurred if the degree of concentration of neutral red in the gastric juice was estimated by different technicians.

OBSERVATIONS

I. Neutral red excretion in individuals with apparently normal gastric function

In addition to observations on the excretion of neutral red in 39 individuals with apparently normal gastric function previously recorded (19), the results obtained in a further 51 apparently healthy subjects are reported here. These 90 subjects comprised in the main, medical students, 17–27 years old, in whom there was no clinical evidence of gastric disorder.

The average excretion time for the 90 individuals examined up to the present is 4 minutes, the shortest was one minute, and the longest 9 minutes. The concentration time varied from 7 to 19 minutes, the average being 14 minutes. The maximal intensity of concentrations of neutral red in the gastric juice varied from 4 plus to 6 plus (Fig. 1).

It is concluded that if neutral red appears in the stomach within 9 minutes of injection, and is concentrated to a 4 to 6 plus intensity within 20 minutes, then the excretion is within the limits of normality (Fig. 1).

Fifteen of these normal subjects were examined repeatedly over a period varying from one week to 6 months. These repeated studies of the neutral red excretion and acid secretion in the same subject on different occasions revealed that the secretion of free acid varied widely even though a constant stimulus (0.5 mgm. histamine) was used during each test. The rate of excretion and concentration of neutral red, however, varied only slightly in the same subject on different occasions. The results obtained with the neutral red test were remarkably constant, and always within the limits of normality, although the free acid secretion varied considerably.

This is clearly illustrated by observations on one of the normal subjects (Table I).

Since the rate of excretion and the rate of concentration as well as the degree of concentration of neutral red in normal subjects is so well defined, and since

the excretion remains remarkably constant in the same individual on different occasions, the neutral red test is far more valuable as a test of gastric function and certainly more reliable than is the secretion of acid.

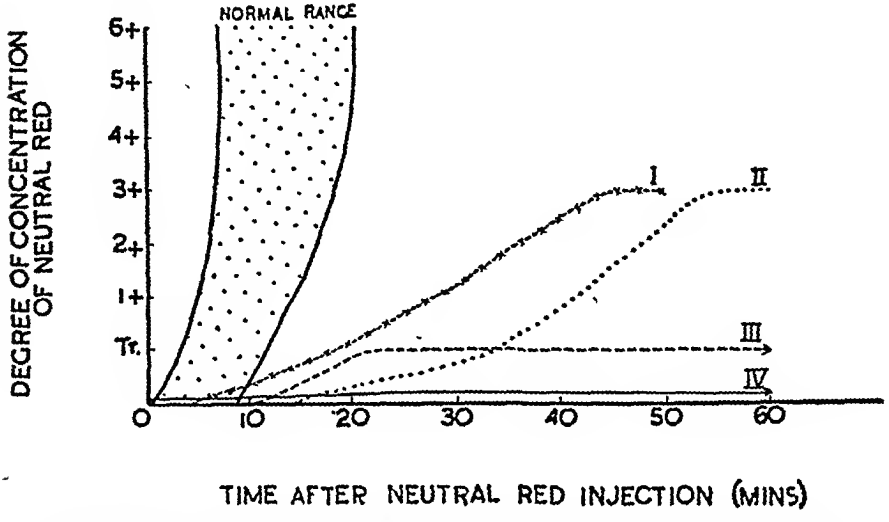

FIG. 1. (Gillman-Neutral red excretion test of gastric function.) Diagramatic representation of neutral red excretion in normal subjects and in cases with gastric dysfunction.

Normal range. Dye appears within 10 minutes of intravenous injection and is concentrated to a 4 to 6 plus intensity within 20 minutes, i.e. Excretion time, 0–10 minutes, concentration time, 6–20 minutes, maximal concentration, 4–6 plus.

Group I reaction. Excretion time, 0–10 minutes, concentration time *more* than 20 minutes, maximal concentration, 3 plus.

Group II reaction. Excretion time more than 10 minutes, concentration time more than 20 minutes, maximal concentration, 3 plus.

Group III reaction. Excretion time more than 10 minutes, concentration time more than 30 minutes, maximal concentration, trace.

Group IV reaction. Dye does not appear at all in gastric juice throughout test period.

TABLE I

Neutral red excretion and acid secretion in the same normal subject on different occasions

NEUTRAL RED SECRETION				FREE ACID SECRETION (MINUTES AFTER HISTAMINE)		
Date	Excretion time	Conc. time	Maxim. conc.	10	20	30
	min.	*min.*				
16/2/43	2	10	6+	56	68	64
17/3/43	2	11	5+	0	10	0
4/4/43	2	13	4+	0	15	23
21/6/43	2	10	4+	63	98	74

Free acid expressed as cc. N/10 HCl per 100 cc. gastric juice.

II. Excretion of neutral red in individuals with disturbed gastric function

The 65 cases which have been selected here demonstrate clearly the variations in neutral red excretion which have been encountered in subjects with gastric

disease, and provide sufficient data to establish the value of the neutral red test as an indicator of gastric function (Tables II, III, IV). Of these 65 subjects, 54 manifested complete histamine anacidity on one or more occasions. Fifteen of these 65 patients presented themselves at the hospital with symptoms of gastric disorders, such as gastric ulcers, acute or chronic alcoholic gastritis,

TABLE II

CASE NO.	CLINICAL DIAGNOSIS	EXCRETION OF NR	HIGHEST TOTAL ACID VALUES		CONCLUSIONS (GROUP IV REACTIONS)
			With NR	With histamine	
1	Gastritis	Never	4	15	Achlorhydria
2	Gastritis	Never	5	7	Achylia
3	Gastritis (alcoholic)	Never	10	10	Achlorhydria
4	Chronic nephritis	Never	16	14	Achylia
5	Diabetic	Never	22	41	Achlorhydria
6	Diabetic	Never	28	21	Achlorhydria
7	Diabetic	Never	47	50	Achlorhydria
8	Diabetic	Never	13	9	Achlorhydria
9	Diabetic	Never	24	32	Achlorhydria
10	Diabetic	Never	17	21	Achylia
11	Diabetic	Never	10	23	Achlorhydria
12	Diabetic	Never	14	24	Achlorhydria
13	Diabetic	Never	19	39	Achlorhydria
14	Asthma	Never	9	13	Achlorhydria
15	Gastric carcinoma*	Never	12	7	Achlorhydria
16	Gastric carcinoma*	Never	9	9	Achlorhydria
17	Gastric carcinoma*	Never	18	18	Achylia
18	Myxoedema	Never	6	8	Achlorhydria
19	Amoebic hepatitis	Never	16	20	Achlorhydria
20	Amoebic hepatitis	Never	12	21	Achlorhydria
21	Pernicious anaemia	Never	11	17	Achylia
22	Pernicious anaemia	Never	11	6	Achylia
23	Pernicious anaemia	Never	6	6	Achylia
24	Pernicious anaemia	Never	8	8	Achylia
25	Pernicious anaemia	Never	10	13	Achylia
26	Severe avitaminosis	Never	12	17	Achlorhydria
27	Severe avitaminosis	Never	8	10	Achlorhydria
28	Severe avitaminosis	Never	21	23	Achlorhydria
29	Severe avitaminosis	Never	14	18	Achlorhydria
30	Severe avitaminosis	Never	16	17	Achlorhydria

* Confirmed at operation.

etc., the remainder were suffering from acute or chronic diseases known to be associated with gastric dysfunction, e.g. pernicious anaemia, nephritis, liver disease, or severe, clinically recognisable avitaminosis. In the latter group are included 14 Bantu patients admitted to the Non-European Hospital, Johannesburg. These subjects, in view of their poor social and economic

TABLE III

CASE NO.	CLINICAL DIAGNOSIS	TIME OF NR EXCRETION IN MINUTES		MAXIMAL INTENSITY OF NR CONCENTRATION	HIGHEST FREE ACID VALUES		REMARKS ON NR EXCRETIONS
		Excretion time	Concentration time		With NR	With histamine	
31	Congestive cardiac failure	12	29	2+	20	22	Delayed and poor concentration (Group II)
32	Alcoholic gastritis	16	35	2+	10	30	First appearance and concentration delayed (Group II)
33	Gastritis	14	40	3+	0	98	Maximal concentration only 10 min. after histamine (Group II)
34	Gastritis and migraine	14	38	3+	0	10	Maximal concentration only 18 min. after histamine (Group II)
35	Sprue	7	43	2+	0	36	Delayed and poor concentration (Group I)
36	Gastritis	5	60	2+	0	32	Traces only 5–60 min. max. conc. 30 min. after hist. (Group I)
37	Gastritis	2	35	1+	0	0	Concentration poor even after histamine (Group II)
38	Gastric ulcer-cancer*	7	70	2+	0	12	Traces only 7–70 min. (Group II)
39	Gastric ulcer-cancer*	7½	44	1+	0	20	Concentration poor even after histamine (Group II)
40	Gastritis	12½	Never	—	0	0	Traces only in flecks of mucus 12½–20 min. (Group III)
41	Microcytic anaemia	30	Never	—	0	0	Traces only at 30 min. Nil thereafter (Group III)
42	Microcytic anaemia	38	Never	—	0	0	Traces only at 38 min. Nil thereafter (Group III)
43	Amoebic hepatitis	23	Never	—	0	0	Traces only at 23 min. Nil thereafter (Group III)
44	Hepatic cirrhosis	45	Never	—	0	0	Traces only at 45 min. Nil thereafter (Group III)
45	Nephritis (acute)	65	Never	—	0	0	Traces only at 65 min. Nil thereafter (Group III)
46	Nephritis (chronic)	17	Never	—	0	0	Traces only at 17 min. Nil thereafter (Group III)
47	Nephritis (chronic)	11	Never	—	0	0	Traces only at 11 min. Nil thereafter (Group III)
48	Epilepsy	36	Never	—	0	0	Traces only at 36–60 min. Never concentrated (Group III)
49	Gastritis	65	Never	—	0	0	Traces only at 65 min. Never concentrated (Group III)
50	Hepatic cirrhosis	90	Never	—	0	0	Traces only in alkaline medium (Group III)
51	Congestive cardiac failure	30	Never	—	0	0	Traces only at 30 min. Nil thereafter (Group III)
52	Cholecystitis	65	Never	—	0	0	Traces only at 65 min. Nil thereafter (Group III)
53	Severe avitaminosis	45	Never	—	0	0	Traces only at 45 min. in alkaline medium (Group III)
54	Diabetic	40	Never	—	0	0	Traces only at 40 min. in alkaline medium (Group III)

* Confirmed at operation.

TABLE IV

CASE NO.	CLINICAL DIAGNOSIS	TIME OF NR EXCRETION IN MINUTES		MAXIMAL INTENSITY OF NR CONCENTRATION	HIGHEST ACID VALUES				REMARKS ON NR EXCRETIONS
					With NR		With histamine		
		Excretion time	Concentration time		Free	Total	Free	Total	
55	Acute alcoholic gastritis	30	70	2+	0	34	0	45	Excretion and concentration delayed (Group II)
55a	Repeat after 4 weeks	12	20	4+	0	39	18	62	Marked improvement. Almost normal (Group I)
56	Amoebic hepatitis			—	0	26	0	26	No NR for 200 min. after 3 × 0.5 mgm. hist. (Group IV)
56a	1 week after 56	60		—	0	36	0	42	NR in traces only at 60 min. (Group III)
56b	2 weeks after 56	34	60	2+	0	44	0	42	NR appeared sooner and some concentration (Group II)
56c	3 weeks after 56	13	25	4+	10	62	20	70	NR excretion and conc. almost normal (Group I)
57	Gastritis	38		—	0	39	0	44	NR in traces only 38–45 min. (Group III)
57a	4 months after 57	2	8	4+	6	22	38	48	Excretion of NR normal
58	Severe avitaminosis			—	0	19	0	19	NR absent during 120 minute test period (Group IV)
58a	After 11 days treatment	90	100	2+	0	17	0	14	NR excreted and concentrated (Group II)
58b	After 21 days treatment	7	13	4+	10	28	4	24	NR excretion normal
59	Severe avitaminosis			—	0	14	0	24	NR absent during 120 minute test period (Group IV)
59a	After 25 days treatment	25	100	3+	0	26	0	46	NR excreted and concentrated (Group II)
60	Severe avitaminosis			—	0	16	0	12	NR absent during 120 minute test period (Group IV)
60a	After 14 days treatment	60		—	0	15	0	24	NR excreted but not concentrated (Group III)
61	Severe avitaminosis	45	60	2+	0	21	0	26	Delayed excretion and poor concentration (Group II)
61a	After 14 days treatment	10	19	5+	14	28	17	30	NR excretion normal.
62	Severe avitaminosis	35	45	2+	0	20	0	28	Excretion and concentration delayed (Group II)
62a	After 17 days treatment	5	27	4+	10	34	18	41	Excretion more rapid. Better concentration (Group I)
63	Severe avitaminosis	5	33	3+	10	31	72	87	NR concentration poor and delayed (Group I)
63a	After 14 days treatment	1	6	5+	36	54	117	124	Rapid excretion and concentration
63b	After 4 weeks treatment	2	12	5+	32	60	54	75	NR excretion normal
64	Severe avitaminosis	5	60	5+	0	30	73	92	NR excreted, but conc. only after histamine (Group II)
64a	After 3 weeks treatment	2	8	5+	10	40	55	79	NR excretion and concentration normal
65	Severe avitaminosis	15	40	1+	0	7	10	21	Excretion and conc. delayed. Poor conc. (Group II)
65a	After 3 weeks treatment	2	7	5+	12	26	40	53	NR excretion and concentration normal

status, always showed clinical signs of multiple deficiencies, but in every instance evidence of pellagra was present. It was possible to examine several of these individuals repeatedly, before, during and after replacement therapy, and to record the changes in gastric mucosal activity accompanying the improvement in their condition (Table III, cases 55–65). The diagnosis in the other cases recorded here was established on clinical, radiological, haematological or other relevant laboratory evidence, and in several instances by the findings at operation.

In every one of the 65 cases with disturbed gastric function recorded here, the excretion of neutral red deviated from the normal in that the dye was not excreted into the stomach at all during the test, or the excretion and/or concentration was delayed; furthermore, the dye when it was excreted, was not concentrated to the intensity usually observed in the normal subjects.

The deviations from the normal excretion of neutral red observed in 65 subjects with gastric dysfunction may be grouped into the following categories (see fig. 1):

Group I. The excretion time was normal, but the time taken to attain maximal concentration of neutral red was longer than normal. The degree of concentration of the dye was subnormal. Nine cases recorded here excreted neutral red in this manner (Table III, cases 35–39, Table IV, cases 56C, 62A, 63 and 64).

Group II. The rate of excretion and concentration was slow, and the dye was poorly concentrated, the maximal intensity being 3 plus. Eleven cases exhibited this reaction (Table III, cases 31–34, and Table IV, cases 55, 56B, 58A, 59A, 61, 62 and 65).

Group III. The excretion time was longer than normal, and the dye appeared in traces only, i.e. the gastric mucosa failed to concentrate neutral red. This occurred in 18 cases (Table III, cases 40–54, and Table IV, cases 56A, 57 and 60A).

Group IV. The dye failed to appear in the gastric juice during the 120 minute period of observation. This was observed in 34 cases (Table II, cases 1–30, and Table IV, cases 56, 58, 59 and 60).

It will be observed that all the cases in Groups III and IV were completely achlorhydric, even after stimulation with histamine. Many failed to secrete pepsin, and were therefore classified as gastric achylia. In these patients the finding of a disturbed neutral red excretion confirmed the conclusion, arrived at from other clinical evidence, that the gastric function was abnormal.

Two patients in Groups I and II secreted normal amounts of free acid, despite the existence of a demonstrable gastric lesion (Table III, cases 38 and 39). In these two instances, the neutral red test suggested a disturbed gastric function, and was therefore more valuable than the study of the acid secretion as a

diagnostic procedure. There were several other instances where the presence of clinical evidence strongly suggested the presence of disease in which the acid secretion was normal, and the neutral red excretion abnormal (Table III, cases 31 and 32; Table IV, cases 55, 63 and 64).

The value of neutral red in assessing the state of the gastric mucosa becomes even more apparent from the repeated study of the same patient improving during treatment.

Cases with gastric dysfunction studied repeatedly with the neutral red test may be classified into two groups. The first group of 3 patients was suffering from gastric disturbances associated with toxaemia (Table IV, cases 55, 56 and 57), and the second group of 8 subjects were pellagrins (Table IV, cases 58 to 65). The records of case 56, a patient suffering from gastritis following emetine therapy for amoebic dysentery, reveals the value of the neutral red test in estimating the improvement of gastric function during recovery from toxaemia.

Case 56. Male aged 29 years. Amoebic dysentery. Patient had received emetine treatment for 3 days, and then started vomiting profusely. Examination revealed a large, tender liver. Blood urea was 364 mgm. per cent. At this time a gastric analysis was performed. Neutral red failed to appear during a 200 minute test period, despite the administration of 0.5 mgm. histamine at 30 minutes, 90 minutes and 120 minutes after the injection of neutral red. Free acid also failed to appear. Fluids were administered intravenously, and the patient improved rapidly, the blood urea falling to 64 mgm. per cent. One week after the first gastric analysis, a second was carried out. On this occasion, neutral red appeared in the gastric juice in traces only at 60 minutes, i.e. 30 minutes after 0.5 mgm. histamine had been injected subcutaneously. The dye was not concentrated, and, in fact, after 70 minutes neutral red could no longer be detected in the gastric juice. Free acid was not detected. Two weeks after the first examination a third test was conducted. On this occasion, neutral red appeared four minutes after histamine had been administered. The dye was poorly concentrated to a 2+ intensity at 60 minutes. Thereafter, only traces of the dye appeared in the gastric juice. On the fourth examination, neutral red appeared in the gastric juice 13 minutes after injection, and was concentrated to a 4 + intensity during the next 12 minutes. The dye was present in the gastric juice for a further 30 minutes after its first appearance. Free acid appeared in the gastric juice both before and after histamine. This was the first time that the gastric mucosa had secreted free acid during the entire period of observation.

When the toxaemia was most severe in this patient, both the secretory and excretory functions were completely suppressed. This accounts for the total absence of free acid and neutral red from the gastric juice, even after repeated injections of histamine (i.e. Group IV reaction). The recovery of gastric

function was presaged by the ability of the gastric mucosa to excrete neutral red although the first appearance of the dye was delayed (i.e. Group III reaction); later the stomach not only excreted the dye, but was able to concentrate it (Group II reaction). Three weeks after the first analysis, the stomach could excrete and concentrate neutral red almost normally. Only on this last occasion had the secretory function recovered, as is evident from the presence of free acid both before and after histamine injection. When first examined the absence of both neutral red and free acid indicated the presence of severe gastric damage. While anacidity, after histamine, cannot be regarded alone as conclusive evidence of mucosal damage, the total absence of neutral red from the gastric juice, even after 200 minutes, in the light of our findings, must be considered grossly pathological. The neutral red test was of value not only in establishing the presence of gastric dysfunction, but it also provided the first evidence of recovery, the appearance of the dye in the gastric juice preceding by some weeks the return of free acid. In cases 55 and 57, the neutral red excretion test yielded similar results. However, it would appear that the gastric damage in these two cases was not as severe as that present initially in case 56, since the excretory function was not completely suppressed.

The second group of cases studied repeatedly with the neutral red test were suffering from severe avitaminosis (Table IV, cases 58 to 65). It is known that various degrees of gastric damage occur in severe avitaminosis. Thus, Spies et al. (24) and observers quoted by Jones (25) have demonstrated by gastroscopic observation the presence of atrophic gastritis in pellagrins. Díaz Rubio has recorded cure of achylia gastrica in a large series of pellagrins by administering nicotinic acid (26). Spies and Chinn (27), Sydenstricker et al. (28), Chesley and associates (29) and Williams et al. (30) have all demonstrated abnormalities in gastric physiology in avitaminosis. All these investigators agree that the gastric function can be improved by appropriate replacement therapy. Furthermore, the degree of improvement in the clinical condition can be assessed with considerable accuracy by the blood sugar response to insulin and adrenalin according to the methods of Mainzer (31) and Tscherkes et al. (32). The results obtained with the neutral red test in avitaminosis can be compared with the clinical and biochemical data and the significance of the modifications observed in neutral red excretion and acid secretion can be carefully assessed.

The data presented in Table III are clarified by an analysis of the case histories of two of these pellagrins with gastric lesions, who were repeatedly examined.

Case 58. Male aged 25 years. On admission (1/5/43) the patient was maniacal. The skin on the dorsum of the hands and forearms, and of the neck and ventral

damage was recognised by the disturbance in the excretory function although the secretory activity was not obviously affected.

DISCUSSION

The recent evidence concerning the wide range of acid secretion by normal subjects as well as the fluctuations observed in the same subject on different occasions has shaken the confidence of clinicians in the value of acid secretion as a diagnostic procedure. The method is rapidly losing its popularity. In fact, Schindler and Alvarez (33 and 34) have recently expressed opinions which may be regarded as the death knell of fractional gastric analysis as a clinical test. The present investigation confirms the opinions recorded by numerous investigators concerning the limitations of the study of acid secretion in the diagnosis of gastric disorders, but provides information which promises a new lease of life to a modified form of gastric analysis in the clinic.

In this study it has been established, firstly, that the excretion of neutral red by the normal gastric mucosa is constant in the same subject on different occasions; secondly, that disturbances in dye excretion can be easily recognised, and thirdly, that a disturbed neutral red excretion can be regarded as evidence of gastric dysfunction. For these reasons alone this test deserves recognition as a diagnostic procedure in the clinic.

Moreover, the modified neutral red test has other qualities which make it invaluable both in the clinic and in the laboratory. It is simple, inexpensive, time saving, free from unpleasant reactions, and above all, it is extremely sensitive.

The ease with which this test can be carried out is implicit in the description provided above. Since the diagnosis of normal gastric function can be made within 30 minutes of passing the tube into the stomach, the neutral red test is time saving, and the results can be obtained at the bedside.

The reliability and sensitivity of the test are borne out both by the data presented here and the information available in the literature. In many of the cases (cases 38 and 39) the neutral red test provided conclusive evidence of gastric dysfunction in the presence of inconclusive acid findings. The findings in these subjects confirms similar observations recorded by Lourja (8) and Morrison (21). Later Henning (20) and Winkelstein (35) noted that whereas anacidity was not always associated with gastroscopically visible damage, 100% of cases which failed to excrete neutral red were shown by gastroscopic examination to be abnormal. It has been possible, recently, in this hospital, to have gastroscopic examinations conducted on several subjects.[1] In these individuals the gastroscopic evidence confirmed the findings with the neutral red test.

[1] I am very grateful to Captain B. Koch for conducting the gastroscopic examinations.

The evidence presented by Olleros (18), Lourja (8), Winkelstein (6, 35), Henning (20) and Morrison (21) as well as that recorded here strongly suggests that total suppression of neutral red excretion may be regarded as proof of gastric mucosal damage. Olleros stated that "in progressive atrophy the successive losses (of gastric function) are (a) spontaneous secretion of free hydrochloric acid; (b) the loss of sécretion of hydrochloric acid even when stimulated with histamine; (c) the loss of secretion of total chlorides, and (d) in the last instance, the loss of excretion of neutral red." While the significance of the disturbances in acid secretion (regarded by Olleros as evidence of gastric damage) is open to question, all investigators are agreed that a stomach is abnormal when it is no longer capable of excreting neutral red. According to the observations recorded by Henning (20) and by Winkelstein (35) the gastric lesion must progress to the extent where the excretion of neutral red must be completely suppressed before the lesion can be consistently recognised with the gastroscope. However, the findings of Lourja (8) and Morrison (21) as well as those of the author, make it quite clear that the total suppression of neutral red is preceded by recognisable disturbances in dye excretion. Olleros and Morales (36) consider that it is possible to differentiate the extensive atrophic gastritis in pernicious anaemia from the localised patchy gastritis in sprue with the assistance of the neutral red test. Lourja was able to diagnose gastric carcinoma before the radiological evidence became conclusive. With the improved technique it became possible to assess with considerable accuracy the various degrees of disturbance in the neutral red excretion which precede the stage when the gastric mucosa is totally incapable of excreting the dye. By observing the excretion time, concentration time, and maximal intensity of concentration of the dye by the gastric mucosa it has been possible to diagnose disturbances in gastric function even before the secretion of free acid was significantly suppressed.

The neutral red test is useful not only as a diagnostic procedure, but also as a method of determining the deterioration of gastric function in the presence of a progressing lesion or the recovery under therapy. Thus, Lourja has stated that if repeated examination with the neutral red test reveals a progressive increase in the time taken for injected neutral red to appear in the stomach, then the gastric lesion can be considered to be extending. On the other hand, Henning and Jurgens (37) and Katsch and Kalk (2) have stated that the return of the power to excrete neutral red is the first clinically demonstrable sign of the recovery of mucosal function. The cases described here fully substantiate these observations. The grouping of the different neutral red reactions (Fig. 1) provides a valuable clinical method of recording the neutral red excretion quantitatively, thus facilitating the comparison of results obtained on different subjects and on the same subject on different occasions.

The neutral red test, therefore, if properly applied and interpreted can materially assist in establishing the existence of gastric dysfunction when other known laboratory tests are either too crude or too unreliable for the purpose. Moreover, since it causes no unpleasant reactions, it can be applied repeatedly to the same patient and thus a precise estimate of improvement or deterioration can be made available to the investigator. Our experience has been so gratifying that we have no hesitation in recommending this test.

SUMMARY AND CONCLUSIONS

1. The improved neutral red excretion test, where the rate of excretion and concentration as well as the intensity to which the injected neutral red can be concentrated are recorded, has been shown to be an excellent indicator of the excretory function of the gastric mucosa.

2. This test has been applied to 90 individuals with apparently normal gastric function, and standards of normality have been suggested.

3. In 15 of these normal subjects both neutral red excretion and acid secretion were examined repeatedly over a period varying from one week to 6 months. These repeated studies revealed that the acid secretion fluctuated considerably in the same subject, while the excretion of neutral red remained remarkably constant.

4. From the study of 300 cases with gastric dysfunction, criteria of abnormal neutral red excretion, expressed quantitatively, have been tentatively suggested. A comparison of the neutral red and the acid secretion tests revealed that the neutral red test is not only more reliable but is also more sensitive than the acid secretion test as an indicator of gastric function.

5. Acid secretion and dye excretion do not necessarily parallel one another, either in healthy or abnormal stomachs. It is suggested that acid secretion and dye excretion are indicators of two apparently independent functions of the gastric mucosa.

6. In view of its simplicity, reliability and sensitivity the neutral red test can be recommended as a means of obtaining valuable information concerning the functions of the gastric mucosa both in the clinic and in experimental studies.

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HEPATOMA OF THE LIVER WITH METASTASIS TO BONE OCCURRING IN A PATIENT KNOWN TO HAVE HAD ADVANCED CIRRHOSIS EIGHT YEARS PREVIOUSLY

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INTRODUCTION

In 1934, a 50 year old laborer was admitted to the Graduate Hospital with an intractable duodenal ulcer. Because of lack of response to an adequate medical regimen, subtotal gastrectomy was advised. At operation, however, a small hobnail liver was found and a gastro-enterostomy was performed. At this time, liver function tests revealed no evidences of hepatic dysfunction except for slight dye retention with the 5 mgm. dose of bromsulphalein, a urobilinogenuria of 1:80, and slight hypoproteinemia. Clinically he manifested none of the findings usually associated with portal cirrhosis. He returned eight years later with jaundice, anasarca, and a large mass in the right upper quadrant of the abdomen. A clinical diagnosis of hepatoma of the liver was made, and at autopsy this was found together with portal cirrhosis and metastasis to rib and lung.

Because of the unusual features presented by this patient, we are reporting his case in detail.

CASE REPORT

J. F., an Italian male, 50 years of age, entered the Graduate Hospital on November 20, 1934, complaining of bouts of gnawing epigastric distress, coming two to three hours after meals, and relieved by food and alkalis, for the past ten years. He gave a history of excessive use of alcohol. Nine months before admission, he was seized with sudden severe pain in the epigastrium which caused syncope. He was taken to the Philadelphia General Hospital where a diagnosis of ruptured peptic ulcer was made. Simple closure of a ruptured duodenal ulcer was performed and the patient was discharged several weeks later free of symptoms.

In June of 1934, severe upper abdominal pain returned; this would begin in the evening and last throughout the night, often being accompanied by nausea and occasionally by vomiting, the latter affording relief.

Physical examination showed a thin man. The blood pressure was 150/100. Bilateral inguinal hernias were present.

Examination of the stomach showed rugal hypertrophy and a penetrating posterior wall duodenal ulcer. Gastric analysis showed a grade 3 hyperacidity with traces of occult blood. On a rigid ulcer program only partial relief was obtained. At operation on December 12, 1934, the liver was atrophic. A high posterior gastro-

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enterostomy was done and the post-operative course was uneventful. Liver function studies revealed no dye retention in thirty minutes with the 2 mgm. dose of bromsulphalein. There was 18 per cent retention in thirty minutes with the 5 mgm. dose. The Takata-Ara test was negative. A pathologic urobilinogenuria of 1:80 was found on one occasion, and 2.4 grams of galactose was excreted in the urine in 5 hours after the usual oral dose of 40 grams. The total serum proteins were a little below normal. Gastric analysis post-operatively showed normal acid with bile in all extractions. X-ray examination of stomach and duodenum again revealed exaggeration of the gastric rugae. The patient was discharged on January 11, 1935 on an ulcer regimen and without symptoms.

He was followed for several months in the Gastro-intestinal Clinic and was free of symptoms on a modified ulcer program. His last clinic visit was on April 13, 1935, at which time he showed a urobilinogenuria of 1:80, a negative Takata-Ara, a serum bilirubin of less than 0.2 mgm. per cent, no dye retention with the 2 mgm. bromsulphalein test. He then disappeared from observation for eight years.

He was readmitted to the hospital on February 12, 1943, complaining of abdominal swelling and pain. From the time of his discharge eight years previously until two months before his present admission, he had been in good health, had shown no weight changes of note, and had experienced no recurrence of his former epigastric distress, despite the fact that he continued to use alcohol immoderately and did not adhere to a strict dietary program. Two months before hospitalization, he began to have a dull discomfort felt diffusely over the upper abdomen; this was most marked several hours after eating and was relieved by sodium bicarbonate and vomiting. One week after the onset of this distress he noted ankle swelling which progressed rapidly. Shortly thereafter his abdomen began to swell and he became short of breath.

He gave no history of a change in bowel habit or of the presence of fresh or changed blood in the stools. He had had no hematemesis at any time.

Examination revealed an emaciated man with a questionably icteric tinge to the skin and conjunctivae. Petechial hemorrhages were scattered over the skin. There were many dilated veins over the chest and abdomen, and a few rales were heard in the left lung base posteriorly. The heart was enlarged to the left, the rhythm was regular, and blowing systolic murmurs were heard over the base and apex. The blood pressure was 120/80. The abdomen was markedly protuberant and tympanitic with dullness in both flanks. In the right upper quadrant was a large, irregular, firm, nodular, and somewhat tender mass. This extended downward to the iliac crest and posteriorly to fill the costo-vertebral angle. The testes were atrophic. There was slight pretibial and ankle edema bilaterally, and neurologic examination was negative.

During this admission, the red cell count varied from 4.6 to 5.3 million cell per cu. mm., the hemoglobin ranging from 13 to 14.5 grams. The mean corpuscular volume was 85 cubic micra; mean corpuscular hemoglobin 27 microgamma; mean corpuscular hemoglobin concentration 32 per cent. The Price-Jones curve of erythrocyte diameter was within normal limits. Reticulocytes were 1.6 per cent. The leukocyte count varied from 8200 to 8300 cell per cu. mm., with from 81 to 90 per cent

neutrophiles. Repeated urinalyses were negative and the flocculation and complement fixation test for syphilis were negative. The sedimentation rate (Westergren) was 3 mm. Total serum proteins ranged from 5.36 grams to 4.80 grams, the albumin component varying from 2.52 grams to 2.92 grams per cent. Fasting blood sugars gave readings from 43 to 62 mgm. per cent. B.U.N. was 17 mgm. per cent, plasma chlorides 604 mgm. per cent, plasma carbon dioxide capacity 54 volumes per cent, and cholesterol concentration 256 mgm. per cent. The van den Bergh reaction varied from 0.6 to 10.0 mgm. per cent. The alkaline phosphatase ranged from 7.3 to 1.9 Bodansky units, and the acid phosphatase was 1.0 Bodansky units. The Quick prothrombin on two occasions was 15 seconds and 25 seconds (normal 13 seconds), and the serum lipase was 0.38 cc. of N/20 NaOH. The galactose tolerance test by the oral route was negative.[2] The glucose tolerance test gave values of 60 mgm. per cent at thirty minutes, 104 at one hour, 177 at two hours, 189 at three hours, 127 at four hours, and 118 at five hours. There was from 15 to 22 per cent dye retention with the 2 mgm. bromsulphalein test. The Takata-Ara and cephalin flocculation tests were both positive. The stools were repeatedly negative for occult blood, and the gastric analysis was within the limits of normal.

X-ray examination of the stomach and duodenum revealed an exaggerated gastric mucosal pattern and a markedly and persistently deformed duodenal cap, but no ulcer niche was demonstrated; the stoma was functioning well; and changes consistent with the presence of varices in the lower third of the esophagus were demonstrated. The presence of ascites and hepatomegaly were revealed roentgenographically.

The patient was placed on a high vitamin and high caloric diet with parenteral vitamins including vitamin K preparations, despite which the prothrombin time became more prolonged. His abdomen was tapped and 200 cc. of dark blood-stained fluid was removed. The ascitic fluid had a specific gravity of 1.020 and contained 1.6 grams per cent of protein, 0.79 grams per cent of which was albumin; neutrophiles and lymphocytes were present in equal numbers. Microscopic examination of the blocked sediment revealed the presence of erythrocytes, leukocytes, and some larger cells which the pathologist thought were possibly malignant in type. The patient rapidly went downhill, lapsed into coma, and failed to respond to continuous infusions of glucose. He died on February 28, 1943. Autopsy was performed by one of us (H. A. H.) 5 hours after death.

The liver weighed 3670 grams. The right lobe was remarkably enlarged; the left lobe was of about normal size. The surface of the liver was nodular and irregular. In the right lobe, the nodules were whitish and soft and ranged in size up to 3 cm. in diameter. In the left lobe, however, the nodules were brownish in color and smaller in size, varying up to 1.5 cm. in diameter, these nodules resembling those usually seen in classical portal cirrhosis. Here and there on the surface of the left lobe were occasional white nodules similar to those found in the enlarged right lobe. On section practically no brownish hepatic tissue could be seen in the right lobe of the liver, this portion of the liver being composed almost entirely of soft yellow-white tissue arranged in large confluent nodules. Some of the larger nodules contained

[2] This was thought to be due to poor absorption from the gastrointestinal tract.

gelatinous necrotic material, and there were several areas of focal hemorrhage. The cut surface of the left lobe was firm and tough. The lobular markings were prominent, but the lobules varied greatly in size. Scattered throughout the parenchyma of the left lobe were occasional nodules of white tumor tissue.

There was a whitish tumor mass, measuring 3 cm. in diameter, which arose from the left sixth rib and projected into the left pleural cavity. The mass was soft, and on section it could be seen that the rib had been eroded by tumor tissue for a distance of 7 to 8 cm., a pathologic fracture being present.

The inferior vena cava, the splenic vein, and the hepatic vein were negative throughout, but the portal vein, as it tunnelled through the liver, contained a plug

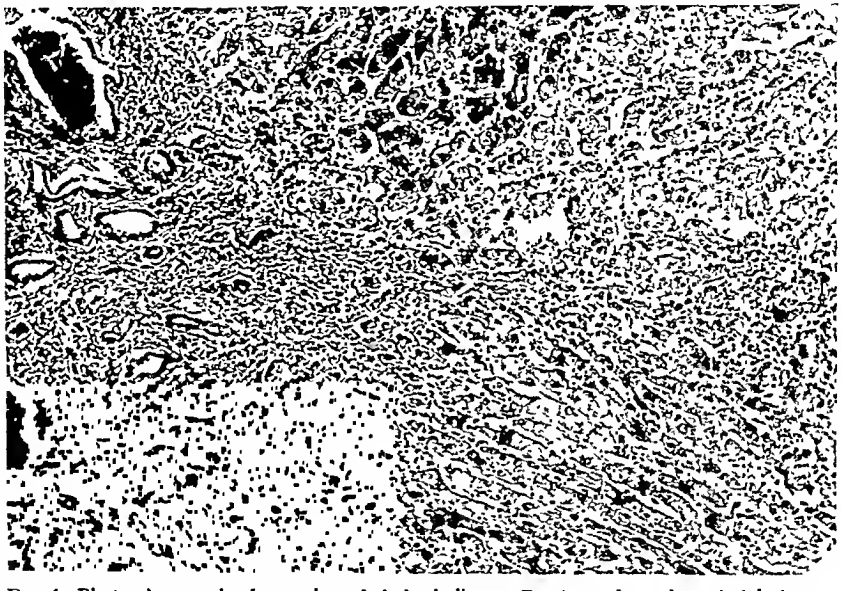

FIG. 1. Photomicrograph of a section of cirrhotic liver. Portions of two hepatic lobules can be seen, and at their periphery there is evident a marked increase in the amount of fibrous tissue and the number of bile ducts. (Hematoxylin and eosin—×150.)

of tumor tissue which pouted out into the vein from its attachment deep within the liver proper. The other organs showed no gross metastases or findings of particular interest, and the pancreas was normal in all respects.

Microscopically, the hepatic tumor tissue was composed of basophilic polyhedral cells arranged in wide trabeculae, in nests, and in some places in strands. The cells varied considerably in size, the majority of the tumor cells being smaller than the cells of the adjacent hepatic parenchyma. The nuclei were large, both hyperchromic and vesicular varieties being present, and nucleoli were prominent. Many cells were multinucleated and a number of mitotic figures were seen. The supportive stroma consisted of wide bands of fibrous tissue. In the central portion of the larger tumor masses degenerative changes and necrosis were evident. No blood vessel invasion by the tumor cells was seen.

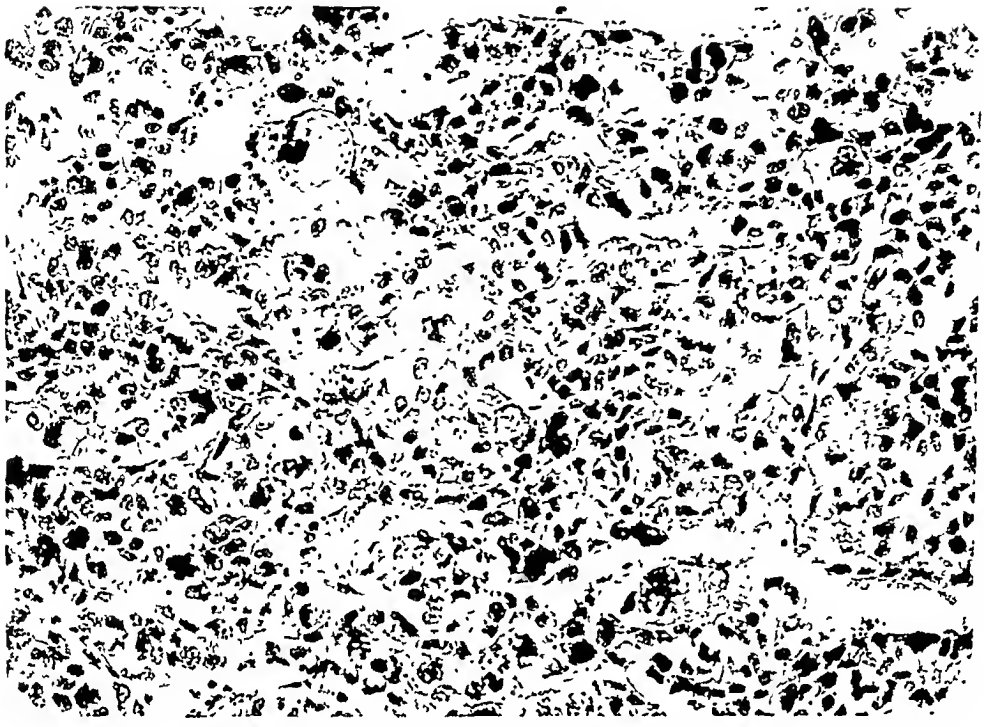

FIG. 2. Photomicrograph of a section of tumor tissue from the liver. Two mitotic figures are present. (Hematoxylin and eosin—×330.)

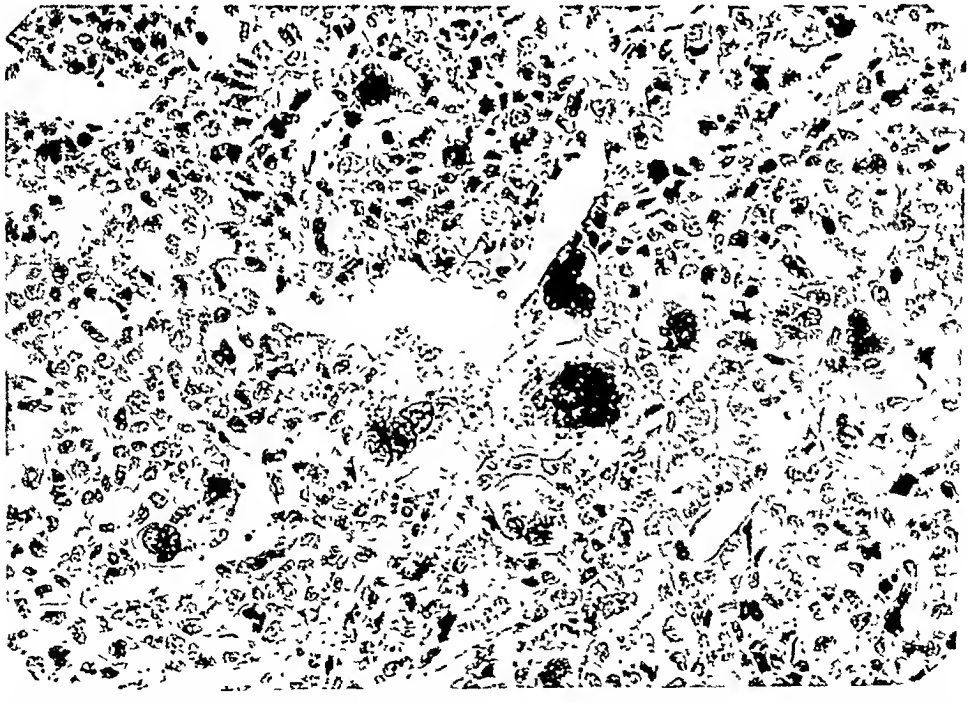

FIG. 3. Photomicrograph of a section of tumor tissue from the liver. Several multinucleated cells can be seen in the center of the field. (Hematoxylin and eosin—×330.)

The hepatic parenchyma adjacent to the tumor tissue was compressed and atrophic, and fibrosis was evident The architecture of the liver proper was markedly abnormal The lobules varied greatly in size and were ringed with fibrous tissue in which small mononuclear cells and bile ducts were found. In many areas the small round cell infiltration involved large portions of the lobules The normal relationship of the venous channel in the central portion of the lobules to the bile ducts, the branches of the hepatic artery, and the radicles of the portal vein no longer was evident. Congestion of the lobules was present.

Examination of the rib lesion revealed the bone marrow to be crowded with malignant tumor cells which showed the same morphologic characteristics as the tumor

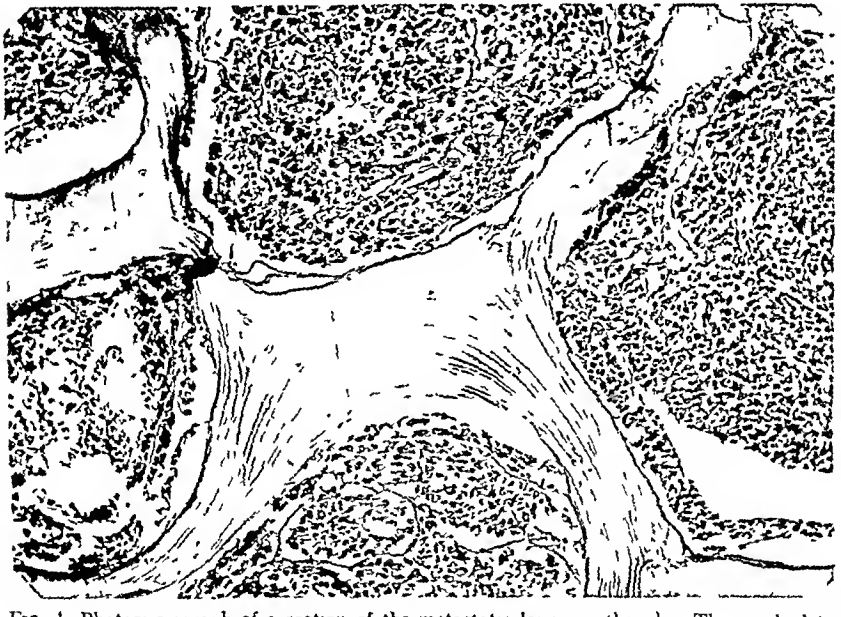

FIG 4 Photomicrograph of a section of the metastatic lesion in the rib The myeloid tissue between the bony trabeculae has been completely replaced by masses of tumor cells (Hematoxylin and eosin—×150)

cells of the liver In one section taken from the lungs, a small blood vessel was found which contained a mass of tumor cells similar in all respects to those found in the liver. The splenic pulp was markedly congested and large dilated sinuses filled with blood were prominent The pancreas showed no abnormalities

Pathologic Diagnosis: Portal cirrhosis, Hepatoma of the liver with metastasis to rib and lung.

DISCUSSION

A number of features in this case are worthy of brief comment

The absence of abnormalities in a number of tests of liver function and the

absence of any of the clinical features commonly encountered in cirrhosis at a time when the liver of this patient was frankly cirrhotic is of interest. The patient showed a pathologic urobilinogenuria, a slight hypoproteinemia, and some retention of dye with the 5 mgm. dose of bromsulphalein. On the other hand, the Takata-Ara and the galactose tolerance tests were negative and there was no dye retention with the 2 mgm. dose of bromsulphalein. These findings serve to emphasize the now well-known fact that any given test of liver function may be negative despite the presence of a frankly cirrhotic liver.

There are to our knowledge no references in the literature to the length of survival of patients following the demonstration of a frank cirrhosis of the liver in the absence of clinical or laboratory evidences of hepatic decompensation. The usual figures given for the duration of life in patients with portal cirrhosis are all calculated from the time of onset of symptoms or findings to which the hepatic disease has given rise. It is important, however, for it to be realized that the existence of a cirrhotic liver may well antedate by a considerable number of years the manifestations of clinical portal cirrhosis.

The relationship between malignant primary tumors, especially hepatoma, and cirrhosis of the liver is striking. According to the consensus of a number of observers, upwards of 75 per cent of cases of hepatomas are associated with cirrhosis (3, 4, 10, 11). Whether an antecedent cirrhosis plays a role in the subsequent development of the carcinoma, as is the belief of most observers, or cirrhosis follows carcinoma, as Wegelin propounded (8), or whether the two conditions occur independently cannot, of course, be determined by this case alone. However, this report does emphasize the association of the two conditions and in this one instance, at least, conclusively shows that the cirrhosis preceded the hepatoma by at least several years.

The presence of metastasis to bone in cases of hepatoma of the liver is commonly thought to be extremely rare. Isolated case reports have appeared in the literature, and Bolker and his associates (1), in a review of the literature up to 1936, could find only nine such cases. Greene (5), however, in 1939, in a ten year collective review of 386 cases of hepatoma, found that metastasis to bone occurred in eight per cent. Since then, several additional cases have appeared in print (6, 9). It is apparent therefore, that although osseous metastasis from hepatomas is not common, it occurs, nevertheless, not so rarely as is ordinarily supposed.

Of interest is the persistent hypoglycemia and the terminal coma, evidently hypoglycemic in origin, which this patient showed. So far as can be determined, only two previous case reports of hepatoma characterized by clinical hypoglycemia are to be found (2, 7).

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LYMPHOSARCOMA OF THE STOMACH: A GASTROSCOPIC REPORT[1]

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INTRODUCTION

A survey of the literature since 1933 (1), when the gastroscope first came into frequent use, reveals that only rarely has the endoscopist observed a lymphosarcoma of the stomach.

The incidence of lymphosarcoma of the stomach is low. Reports appearing in current literature reveal that approximately one to two per cent of all primary gastric malignancies are non-epithelial tumors. Madding (2) indicates that only 428 cases of non-epithelial tumors of the stomach had been reported to 1938. Balfour and McCann (3), in a series covering the years 1908–1928, state that the ratio of sarcoma of the stomach to carcinoma of the stomach is 1:159. They report 54 sarcomas, of which 32 were lymphosarcomas. Cameron and Breslich (4) give the incidence of sarcomas of the stomach of lymphoid origin as 45 per cent of all sarcomas, about three-fourths of which they report as lymphosarcomas. It is difficult to estimate the incidence of stomach lymphosarcoma because of the confusion which exists in nomenclature. Among the many terms used to describe lymphosarcomas are found the following: malignant lymphoma, malignant lymphoblastoma, sarcoma, lymphogranuloma, and aleukemic leukemia.

Six patients with lymphosarcoma of the stomach have been examined gastroscopically. Two (5) types of the disease have been described, the diffuse and the circumscribed. To this group we wish to add the following patient, the first in our series of 900 gastroscopic examinations:

CASE REPORT

H. M., 42-10042, was first admitted to the University Hospitals on August 26, 1942. He was a 66-year-old white farmer. In November, 1941, he noted a small lump in the left epitrochlear region which gradually increased in size until, seven months later, it opened spontaneously and started to drain a clear, watery fluid. There was no history of trauma or of contact with rabbits. His past history was uneventful, except for an appendectomy in 1915. He had no abdominal distress at that time.

On examination the patient's skull was negative. He had bilateral arcus senilis, and bilateral hearing loss was noted. The jaws were edentulous. The thyroid was not enlarged. The thorax was symmetrical, and the lungs were normal to examination. The heart was thought to be slightly enlarged; however, no murmurs nor

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irregularities were present. The blood pressure was 240/140 mm. of mercury. There were no abnormalities of the abdomen; the rectum was normal; and the prostate was not enlarged. In the left, anterior, cervical chain there was an enlarged lymph node, and there were enlarged, firm, discrete, non-tender nodes present in both axillary regions. On the medial aspect of the left elbow, extending over the lower part of the upper arm, was an indurated, inflamed swelling measuring about 8.5 by 5 cm. This swelling was surmounted by a papilla of granulation tissue at the orifice of a sinus from which dripped serous fluid. Just superior to this sinus was a fluctuant swelling. No portion of the area involved was found to be tender.

The urine was negative. The blood Wassermann, Kahn, and Kline tests, also, were negative. The hemoglobin was 10.5 grams per cent (Haden-Hauser). The leukocyte count was 5,050; and the blood smear was found to contain 40% polymorphonuclear leukocytes, 55% lymphocytes, 2% eosinophils, and 3% unclassified cells. Roentgenogram of the arm revealed an inflammatory process in the soft tissue with no evidence of bone involvement. Roentgenogram of the chest gave no evidence of mediastinal tumor. The discharge from the sinus was cultured and was found to contain a hemolytic staphylococcus, but no actinomyces or acid-fast organisms were found.

On September 11, 1942, the lesion was excised. No attachment to bone was demonstrated. The lesion was, however, adherent to periosteum, muscles, and vascular sheath. The pathologist reported that the lesion was a neoplasm of lymphoid origin involving extensive destruction. Post-operatively, the patient was given radiation therapy consisting of 1200 Roentgen units. The wound healed uneventfully, and the patient was discharged from the hospital on September 24, 1942.

The patient returned to the hospital November 24, 1942. He stated that there had been slight drainage from the incision for a while, but that this had ceased. The incision was well healed, and further roentgen therapy was not thought to be necessary.

On February 24, 1943, the patient was admitted for the third time. He then stated that he had developed dull, burning, gnawing pain in the epigastrium. There had been no constant relation of this pain to ingestion of food. The pain had not radiated, and the attacks had lasted one to two hours. He had lost approximately eight pounds in weight. There had been no nausea or vomiting. Physical examination revealed no new significant features. The surgical scar on the left arm was well healed. The urine was again negative. The erythrocyte count was 3,620,000, and the hemoglobin was 8.9 grams per cent (photoelectric method). The leukocyte count was 8,450, the differential count showing 68% polymorphonuclear leukocytes, 24% lymphocytes, 3% eosinophils, and 5% monocytes. A progress film of the chest showed no change, and roentgenograms of the stomach and duodenum following barium by mouth were interpreted as normal.

On February 26, 1943, the patient's stomach was examined with a gastroscope, the instrument being introduced with ease. In Depth 1 the antrum and pylorus appeared normal. As the instrument was rotated to the 6 o'clock position, a wall

and some ulcerated mucosa could be seen. The instrument was withdrawn to Depth 2 where the mucosa of the anterior wall appeared somewhat paler than normal. On the greater curvature, extending to both the anterior and posterior walls, there was an ovoid lesion about 4 cm. long and 3 cm. wide which had a sharply elevated, dusky red retaining wall about 1 cm. high. The center of the lesion was partly ulcerated, and there was some bleeding in the wall itself. The entire lesion had the appearance of a flat, saucer-shaped mass saddling the greater curvature. Just posterior to this mass adherent mucous and submucosal hemorrhages were noted. The gastroscopic impressions were:

1. (a) Carcinoma of the stomach in the midportion, or
   (b) Lymphosarcoma of the stomach, and
2. Superficial gastritis.

A subtotal gastrectomy was performed on March 1, 1943, about four-fifths of the stomach being removed. Gross examination revealed a circumscribed, ulcerated area high in the middle third of the specimen. There was some injection about this area, and it had a granular, red base. The lesion extended through the wall of the stomach, and there was involvement of the serosa. There was considerable thickening in the area, but there was no hard induration around the ulcer margin. The remainder of the stomach had a normal rugal pattern, and appeared to be essentially normal throughout.

Microscopically, the lesion revealed superficial ulceration with acute inflammation. The mass proper consisted of neoplastic cells which were densely packed. There was a minimal amount of diffusely dispersed supporting stroma. The neoplastic cells had extensively infiltrated and had largely replaced the normal gastric wall. There was no evidence of arrangement of the neoplastic cells into any structural pattern, or of any secretory activity. The individual cells were rounded and contained rather large nuclei. They appeared to be immature cells of lymphoid origin. A few eosinophilic leucocytes were present, but other histologic evidence of Hodgkin's Disease was lacking.

Impression: Malignant lymphoma of stomach.

The post-operative course was uneventful, and the patient was discharged from the hospital on March 17, 1943.

COMMENT

At the time of the gastroscopic examination we were cognizant of the report of the pathologic lesion on the patient's arm. The possibility of lymphosarcoma of the stomach was discussed. However, it was decided that, in fairness to the patient, it must be reported as a carcinoma of the stomach. Because of the development of such a large lesion in an apparently short period, we were unwilling to take the risk of waiting for evidence of regression following roentgen therapy.

It is worthy of note that the lesion was not seen by the roentgenologist. Following gastroscopy a repeat roentgenological examination was requested

but, through oversight, this was not done. Although it seems probable that the lesion might have been demonstrated by this method, this is the first case of lymphosarcoma of the stomach in which surgical excision was performed on gastroscopic indications alone.

From the standpoint of visualization of the lesion with the gastroscope, we do not believe that there were sufficient characteristic features to permit unequivocal indentification of the lesion as a lymphosarcoma. The consensus of opinion in current radiological literature is that there are no positive diagnostic points on roentgen examination. Since these lesions have been reported to be quite radiosensitive, this is perhaps unfortunate. However, we believe that roentgen therapy of any inoperable lesion of the stomach is justifiable on the basis that it might be a lymphosarcoma, which might, under such treatment, become operable.

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THE INTRALOBULAR PANCREATIC CIRCULATION

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INTRODUCTION

The state of our knowledge concerning the circulation within the pancreatic lobule is incomplete. It has not been decided whether all the blood going to acinar tissue has first passed through insular structures (1, 2) or whether only part of it follows this course before reaching the acini (2, 3). Development of a satisfactory injection method (4) which had been previously applied by Shonyo (5) to kidney and Du Mais (6) to liver in as yet unpublished work suggested the use of neoprene in a study of the circulation through pancreatic acini and islands of Langerhans. Application of previous injection-corrosion methods to the pancreas had been unsuccessful (1) or had not included capillaries (7). With these thoughts in mind the pancreases of dogs, cats, rabbits, guinea pigs and white rats were examined.

METHOD

Animals were bled while they were under ether anesthesia and were injected immediately or within thirty minutes after the heart action had stopped. Arteries were first washed with 0.9 per cent solution of sodium chloride and then injected with neoprene (100 per cent) or neoprene black (neoprene 80 per cent, India ink 20 per cent) from a syringe at temperatures of 45° to 55°C. The injection mass was introduced into the descending thoracic aorta with clamps on the abdominal aorta between the celiac axis and superior mesenteric artery, on the proper splenic vessels and on the hepatic artery near the liver. In conjunction with arteries either veins (via the superior pancreaticoduodenal vein) or ducts were injected with a contrasting colored mass.

After injection the pancreas was hardened in situ by covering it with alcohol sponges and then was dropped into commercial concentrated hydrochloric acid. Next day the viscus was washed with running water to remove corroded tissues. A rubber cast of vessels and ducts remained. Dissection of the cast was carried out under a binocular microscope at magnifications up to 100 diameters.

Small pieces of each hardened mass impregnated pancreas were placed in ninety-five per cent alcohol. Next day frozen sections (20–40 microns) were made and examined in glycerin after staining the neoprene white with

sudan III. Thick sections of the same small, alcohol hardened pieces were cut with a razor and treated by the histocorrosion technic of Du Mais. In this method the thick section is observed continuously in glycerin while the tissues are corroded away with strong hydrochloric acid. By this device vascular structures in the neoprene cast can be identified as the other tissues are gently pushed away after the proper orientations of vascular structures to translucent nonvascular ones have been made. Differential staining of islets with neutral red and of ducts with pyronine (8, 9) was also employed to aid identification of islets.

RESULTS

Examination of the cast gives a three dimensional view of the circulation. Grossly, the cast resembles the form of the organ most faithfully. When examined under low power, single lobules were seen to be made up of a fine feathery capillary mass (fig. 1, top). In doubly injected specimens this represented the extremely fine capillary network surrounding the contrasting colored veins which drained the region. Some specimens in which arteries and ducts were injected enabled this capillary mass to be identified as the acinar capillary bed which crowns the contrasting mass of the ducts. To preserve this capillary bed great care was necessary in washing away the corroded glandular and other tissues. These capillaries were so exceedingly fine that vigorous washing would break them off and leave a cast consisting, of vascular branches down to arterioles. Such vigorously washed casts were, however, useful to study arteriolar distribution. The plan of distribution (fig. 2) of arterioles and venules in a well-washed specimen indicates that the arteries and veins accompany one another up to the acinar capillary bed. This arrangement of arterioles with terminal fine capillary network resembled a well-kept buckthorn hedge in wintertime (fig. 3). Arterioles reaching any segment of capillary bed had free anastomosis with adjacent arterioles (fig. 4). By this injection method one could begin at the interlobular artery and follow a vessel down to the terminal arborizations of the intralobular capillary vessels. Anastomoses between capillary beds served by different arteriolar twigs were observed frequently.

Capillaries of the islets of Langerhans could be injected only from the arterial side while acinar capillaries could be injected from either arteries or veins. This is true even though veins are injected first in doubly injected specimens. Intralobular arterioles pass to the acinar capillaries, going either via islet tissue or by direct routes. Under low power, islets appear as glomeruli of varying size scattered through the acinar capillary tissues (fig. 5). Using the histocorrosion method the intimate capillary structure (fig. 6) can be seen to be a series of moderately coiled vessels of relatively wide diameter.

FIG. 1. Low power (×6) view of feathery appearance of pancreatic lobules (top) when injected with neoprene white (arteries) and neoprene black (veins) (dog).

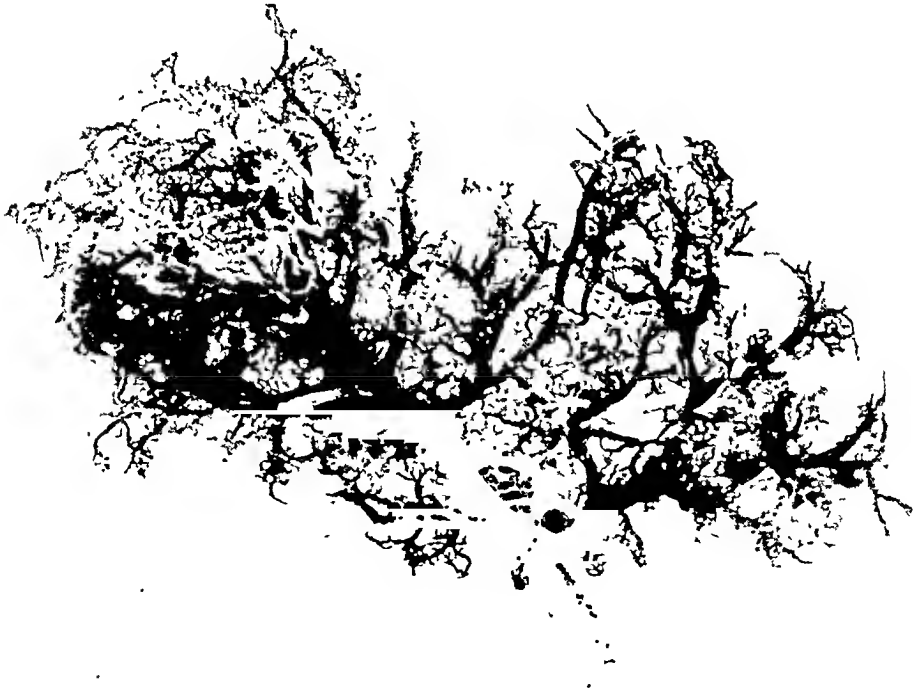

FIG. 2. Well-washed cast showing arteriolar (gray) and venular (black) arrangement (×25) (dog).

FIG. 3 "Buckthorn hedge" appearance of well-washed cast (singly injected, arteries, white) seen best at top of figure (×30) (dog).

FIG. 4. Anastomosis between adjacent arterioles within a single lobule. Singly injected cast, neoprene black (×50) (dog).

FIG. 5. General view of doubly injected cast (arteries white, veins black) showing islets of varying size appearing as white glomeruli throughout the acinar mass (×21) (dog).

Frozen sections stained with sudan III gave similar results. In a carefully washed specimen under highest magnification (fig. 7) it was possible to distinguish the islet capillary network enclosing corroded islet tissue.

COMMENT

The extent of the capillary bed by this method is so great that it may be suggested that the maximal possible field is represented. Indeed the cast of the vascular tree resembles the intact organ very closely when seen macroscopically. Anastomoses between acinar arterioles and also between the recipient capillary regions would tend to insure adequate circulation under widely varying circumstances in the species studied.

Islets vary in size and are placed entirely on the arterial side of the circulation confirming the previous observations of Wharton. Blood may reach the acini either via islet tissue or directly, as dissections beginning at interlobular arteries and ending at intralobular capillaries have shown.

It is interesting that the histocorrosion-neoprene injection technic gives results confirming the conclusions on the islet form (10) and the afferent insular supply (10, 11) obtained by different methods. Furthermore, vigorous washing (which removes fine capillaries) produced a cast of arterioles and arteries as obtained by celluloid technics (7).

CONCLUSIONS

As a result of study of the intralobular pancreatic circulation after injection of neoprene and corrosion of pancreatic tissue, the following conclusions were drawn:

1. Anastomoses exist between intralobular arterioles and also between acinar capillary fields fed by different arterioles within any one lobule.
2. Blood may reach acinar capillaries via islets of Langerhans or directly without passing through insular tissue.
3. The potential intralobular capillary circulation is very large.

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EDITORIALS

DIVERTICULOSIS AND DIVERTICULITIS OF THE COLON

It would seem as if today no well-trained physician should confuse diverticulosis of the colon, which occurs in perhaps 5 per cent of persons past forty, and which is usually, if not always, symptomless, with diverticulitis, a rare disease, and one that sometimes has serious import for the patient. And yet, every consultant who spends his days reading letters of findings brought in by patients knows that sometimes even well-trained physicians will seem to have the two conditions confused: they will write as if they could see no difference between the mere presence of the little pouches and the presence of serious inflammation in and around them.

Actually, such confusion is to be expected so long as authorities continue to state or infer that diverticulosis causes all sorts of indigestion and abdominal distress. It may be perfectly true that 25 per cent of the patients have constipation, 20 per cent have a sore colon, 15 per cent have flatulence, and so on, but how can this mean anything when 1000 patients taken consecutively in a gastroenterologist's office will show similar incidences of these symptoms? The fact that practically never are there any adhesions around the diverticula makes it appear that very seldom do they become inflamed enough to produce symptoms, and Rankin and Brown, in perhaps the best documented study ever made of the subject, concluded that ordinarily they do not cause distress. Much against their being responsible for symptoms is the fact that many of the persons found to have a score or two of these little pouches along the colon have a comfortable abdomen and normal bowel movements. This being so, it is doubtful if a physician should ever show a patient the roentgenographic shadows of his diverticula and say, "There is the cause of your trouble." It is doubtful also if he need prescribe any treatment or utter any warnings about dangers ahead.

Often it would be a kindness not to tell an elderly man or woman about the few little diverticula that have been found because about all this information can do is to cause alarm, but usually the physician will feel that he must report the finding if only to protect his reputation; if he should fail to make any comment and later other physicians should become aghast over the discovery of the pouches, he would probably be blamed and deemed incompetent or careless.

The diagnosis of diverticulitis is hardly justifiable unless there is a typical story of one or more attacks of pain, cramps, fever, chills, borborygmus, temporary obstruction of the bowel, perhaps irritation of the bladder, or

penetration of this organ by a fistulous tract arising in the bowel. Usually, then, in an attack a mass will be felt on the left side of the abdomen, roentgenograms will show constriction of the colon in the affected region, and sigmoidoscopic examination will show that the pelvic colon is bound down and restricted in its movements.

There appears at times to be an intermediate condition in which there are so many diverticula on a short segment of colon that the bowel in the region is irritated and the lumen narrowed, with attendant soreness and some cramping. In these cases the absence of any increase in the leukocyte count or the blood sedimentation rate, and the absence of fever or a mass or any sign of fixation of the segment will tend to rule out the presence of serious inflammation.

Fortunately, true diverticulitis appears to be a rare disease. Even in a large clinic where over 100,000 patients are seen in a year, an individual gastroenterologist can go from one year's end to another without seeing more than one or two cases.

For many years after diverticulosis of the colon became well known, it was the custom of physicians to warn the patient to be examined every so often because of the danger of cancerous degeneration of the pouches, but after a while some physicians began to wonder why, if this danger was real, they were not seeing cases in which cancer appeared to have begun in this way. About 1928 it occurred to W. J. Mayo that he could hardly remember having seen a case of this type (1) and when Rankin and Brown (2) reviewed much of the Mayo Clinic material, their findings supported Dr. Mayo's impression. In 227 cases of true diverticulitis they found co-existing carcinoma in only four cases, and in 679 cases of carcinoma of the colon, associated diverticulosis was found at operation only four times. In no case was it clear that cancer came because of the diverticulosis. Under these circumstances, the impression was left that diverticulosis must do much to protect the colon from cancer. Evidently, then, it is unnecessary and unfair to worry possessors of diverticula with the thought that they are particularly susceptible to the development of carcinoma. In most cases cancer of the large bowel appears to begin in a polyp.

On looking at a typical colonic diverticulum, lined as it is only by mucosa, and without any muscle about it to push contained feces back into the bowel, one gains the impression that often, because of retention of material in the pouch, it should become irritated, inflamed, and perhaps necrotic, but actually, at hundreds of necropsies, Dr. H. E. Robertson has been impressed with the fact that the wall, both inside and out, is remarkably normal. Histologic study usually fails to show any lymphocytic infiltration of the mucosa, and, as already noted, one very rarely sees adhesions to the serous coat.

Incidentally, it may be worth noting that today many internes and others are still making the mistake of assuming that the word for the little pouch is the Latin feminine noun, diverticula, with the plural, diverticulae. Actually, of course, the noun is the neuter, diverticulum, with the plural, diverticula.

WALTER G. ALVAREZ.

PREVENTION AND REPAIR OF LIVER DAMAGE

The increasing incidence of hepatitis, whether from bacterial or virus infection, from drugs, notably sulfonamides, or from the poisons to which industrial workers are exposed, emphasizes the importance of recent experiments with curative and protective food substances. The recognition that purely nutritional factors may cause hepatic damage in animals suggests that analogous liver diseases in human beings may be prevented by appropriate modifications of diet. Pathologic changes which have already occurred in the liver may be reversed through administration of methionine, cystine and choline, a protein-rich diet and elements of the vitamin B complex in balanced proportions.

Further evidence of the importance of food components in the etiology of liver disease is the association of renal lesions, particularly hemorrhagic cortical necrosis, observed by Paul György (1) in animals with hepatic necrosis and cirrhosis induced by deficient diets.

The prophylactic and curative value of casein for fatty infiltration of the liver, experimentally induced in rats, is due to the methionine and choline in such preparations. Large amounts of fat, with much cholesterol, tend to neutralize the prophylactic value of the methionine or choline. When diets devoid of these protective factors are fed to animals, hepatic necrosis, often with cirrhosis, occurs regularly in the course of one hundred fifty days or less. Rats so fed may be visibly jaundiced, and they may have ascites and pleural and pericardial effusions. The first stage of the acute injury sustained by the liver appears microscopically as focal, parenchymatous degeneration with central necrosis. The lesions resemble those seen in the acute and subacute stages of yellow atrophy in man. The cirrhosis which develops is periportal and eventually simulates Läennec's cirrhosis.

Both cirrhosis and necrosis may be observed frequently in the same liver. The fluorescent pigment ceroid is found in quantity in the liver cells or in the Kupffer cells and possibly represents lipoid material closely combined with protein. Unfortunately, the dietary cirrhosis in rats is not completely analogous to human cirrhosis in that ceroid is not found in the latter.

The protective value of casein, or of cystine and choline, against fatty infiltration of the liver, may depend upon the labile methyl groups in choline and in methionine, respectively. Why methionine alone is capable of pre-

venting hepatic injury while choline seems to require the intermediation of cystine is not clear.

From circumstantial evidence, cirrhosis in human beings would seem to be etiologically similar to experimentally produced liver damage. Alcoholic persons, for instance, commonly ingest little protein and an insufficient supply of B complex factors, including choline. Hepatic injury may perhaps not be produced so much by the alcohol as by the lack of protein and vitamins, as in cases of pellagra and beriberi.

Miller and Whipple (2) showed that fatal liver damage could be produced in dogs fed protein-deficient diets for several weeks when chloroform was administered, and that such damage could be averted by the intravenous injection of 3 gm. of methionine. Carbon tetrachloride induces similar hepatic injury, and Beattie, Herbert, Wechtel and Steele (3) applied Miller and Whipple's findings in the case of a human patient who had accidently swallowed from 30 to 40 cc. of carbon tetrachloride. About eighteen hours afterward the liver was enlarged and tender. Methionine was given by mouth and later by intravenous infusion. The liver promptly shrank, and in 48 hours became insensitive. Symptoms of impending hepatic coma subsided.

Suggestions derived from animal experimentation and now this experience with one patient are as follows:

1. Methionine may be given in doses of from 2 to 4 gm. daily. Cystine and choline given in doses of about 2 to 4 gm. daily are likely to have less effect.

2. A protein-rich diet with a high content of methionine may be used. It may be supplemented with methionine, or cystine and choline.

3. The fat intake should be limited. The least harmful fats are likely to be those rich in unsaturated fatty acids and low in cholesterol.

4. Vitamin B complex should be added to the diet.

Experiments have now progressed to a point where the suggestions derived therefrom may be used as a guide to treatment in the cases of an ever increasing number of patients with infections and toxic hepatitis. The suggestions will help also in the institution of preventive measures for persons who are being subjected to the influence of hepatotoxic substances.

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COMMENT

TRENDS IN THE SURGICAL TREATMENT OF ULCER

Every gastroenterologist who has been in practice for twenty years or more knows that during this time there has been a decided change in his attitude toward the treatment of duodenal and gastric ulcer. Twenty years ago, especially if he was surgically minded, he was inclined to send in for the performance of gastroenterostomy every patient with the disease or at least every patient who was having considerable pain and disability. But about that time he discovered that the results of the operation were not always satisfactory, and in some distressing cases the patient was worse than he was before. As the surgeons often remarked, it was a shame that bad results in some cases had to scare physicians away from using an operation which so often cured spectacularly and permanently. But scared they were, and the result of their fear is shown graphically in figure 1 taken from a recent review article by W. Walters, H. K. Gray, J. T. Priestley and V. S. Counseller (1). There it will be seen that at the Mayo Clinic the percentage of persons with duodenal ulcer operated on fell from around 38 per cent in 1928 to 13 per cent in 1937. Since 1937 the fraction has fluctuated around 16 per cent. Today the only patients with duodenal ulcer operated on at the Mayo Clinic usually have a complicated or intractable type of lesion which (1) is not much helped by medical treatment, (2) is causing much pain or vomiting, (3) has obstructed the pylorus, (4) has penetrated into the pancreas, (5) is bleeding frequently or (6) for one reason or another will not let the patient work or sleep or enjoy life.

Figure 2, also taken from the review by the Mayo Clinic surgeons, shows how during the years there has been a decided trend away from gastroenterostomy and toward partial gastrectomy. The percentage of patients (operated on) in whom gastroenterostomy was performed fell from around 73 in 1928 to 41 in 1942, and it would have fallen still lower were it not for the fact that in some cases of women or older men with pyloric obstruction, who have little tendency to the formation of a new ulcer, this operation was thought to be safe enough. In other cases the bigger operation was avoided for one reason or another. The percentage of partial gastrectomies rose from about 3 per cent in 1928 to 57 per cent in 1942. From 1928 to 1934 pyloroplasty was tried, but evidently the results were not satisfactory because the frequency with which this operation was performed fell from 30 per cent in 1934 to 1 per cent in 1939.

In fairness to the surgeons it must be noted that during these last twenty years their difficulties have increased as physicians have formed the habit

of turning over to them only those patients who have gotten to the end of their medical rope with a severe and intractable type of ulcer. Often these persons are emaciated and in poor shape to stand any operation, and, worse yet, many of them have a strong tendency to develop a new ulcer as soon as the old one is healed. In such cases the obtaining of a permanent cure represents a great

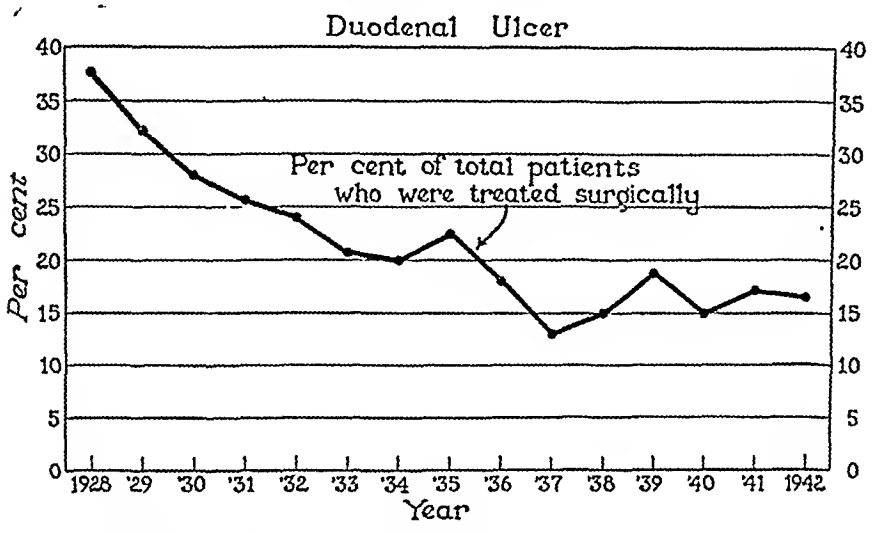

FIG. 1. Percentage of total patients with duodenal ulcer who were treated surgically

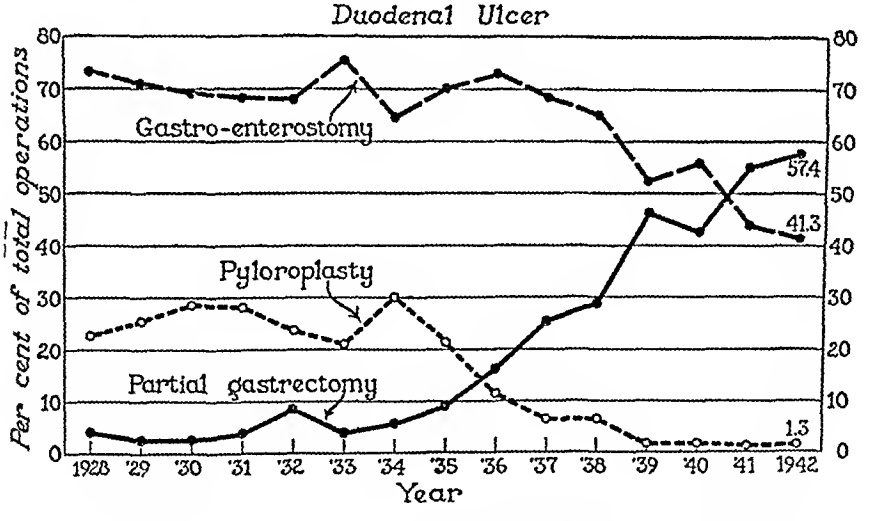

FIG. 2. Percentage incidence of several operative procedures for duodenal ulcer

achievement, and often just the getting of the patient out of the hospital alive represents a triumph of surgical technic.

The sad feature is that as yet no procedure has been found which will enable the physician or surgeon to tell in advance which patient will get a perfect result from gastroenterostomy and which will develop a new and most

distressing ulcer. Many men still keep hoping that the degree of gastric acidity will give them this prognostic information, but the follow-up studies of Vanzant et al. (2) showed no justification for using this criterion.

As regards gastric ulcer, figure 3 from the paper of Walters et al. shows that at the Mayo Clinic, during the years from 1935 to 1938, from 40 to 50 per cent

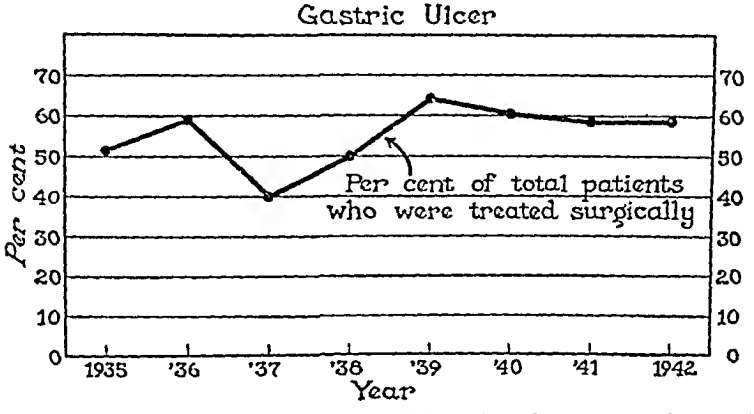

FIG. 3. Percentage of total patients with gastric ulcer who were treated surgically

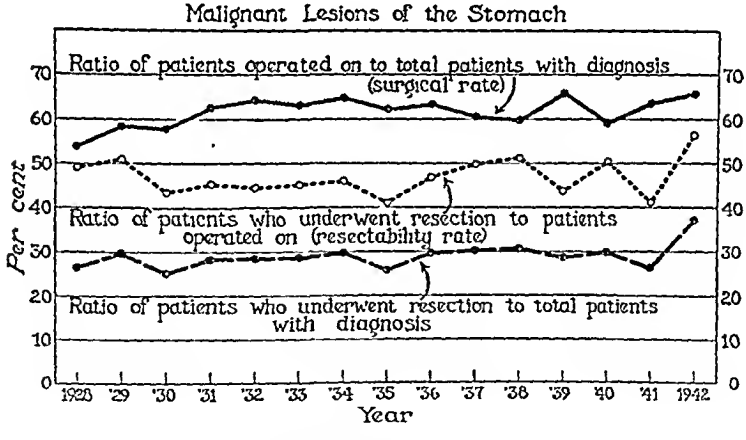

FIG. 4. Malignant lesions of the stomach

of the patients with such lesions have been operated on. The rise to 60 per cent in the years from 1939 to 1942 reflects the increasing consciousness of physicians everywhere that the ulcer-bearing stomach is more than normally subject to the development of cancer.

Very hopeful is the fact that during 1942, at the Mayo Clinic, the hospital

mortality rate[1] for partial gastric resection *for benign lesions* of the stomach and duodenum fell to 1.6 per cent. This compares surprisingly well with the rate in the same institution of 1.5 per cent for gastroenterostomy. Evidently, in many cases, the surgeon *who is performing gastric resections every day* does not have to let fear of the mortality rate of the larger operation affect his decision whether or not to perform it.

In the case of malignant lesions of the stomach, the hospital mortality rate for partial gastrectomy, although markedly reduced of late, is still higher than that in the case of patients with benign lesions; in 1942, at the Mayo Clinic it was 6.7 per cent.

The sad fact is that during the years from 1929 to 1940, in spite of all the efforts that have been made to get patients with gastric cancer into the hands of a good surgeon within a month after symptoms appear, the percentage of cases in which the lesion could be removed has not gone up more than 2 per cent! Until 1941, the figure remained about 30 per cent. It is to be hoped that the rise, in 1942 to 38 per cent means that a better era is dawning (fig. 4).

WALTER C. ALVAREZ.

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[1] Any death occurring while the patient operated on is in the hospital is listed as due to the operation.

BOOK REVIEWS

Gastroenterology. Volume II. By HENRY L. BOCKUS, M.D. 975 pp. W. B. Saunders Company, Philadelphia and London, 1944.

This second volume is as attractive as the first one, the big difference is that the several chapters have been written by some seven co-authors. This volume covers diseases of the small and large bowel, including dysentery of various kinds, and malignant tumors of the colon and rectum. It is good to see a chapter on endometriosis of the colon and rectum, also one on lymphopathia venereum. There is a chapter on melanosis coli which results from the use of anthracene laxatives. Section VI is on diseases of the peritoneum, mesentery and omentum. A good bibliography is attached to each chapter.

The book is beautifully printed and illustrated and conforms to the high standard set by the first volume.

What is hypnosis? Studies in auto and hetero conditioning. By ANDREW SALTER. 88 pp. Richard R. Smith, New York, 1944. $2.00

This little book is hardly an answer to the question on the title page. It deals largely with auto-hypnosis by self suggestion. A number of cases are described in which persons have produced anesthesia in certain skin areas and have almost wiped out perception of sound. There is some information on the technic of teaching persons to hypnotize themselves. Apparently the subjects have no difficulty in getting out of the state.

The reader is likely to keep wondering how safe it is for a person to get into the habit of throwing his brain out of function in this way.

Infections of the peritoneum. By BERNHARD STEINBERG, M.D. 455 pp. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers. New York, 1944. Price $8.00

This is a valuable bacteriologic and clinical study of peritoneal infections. Doctor Steinberg has spent eighteen years studying the problems involved, and his researches here summarized should be of great value to all surgeons, especially those in emergency hospitals who have constantly to cope with peritonitis.

The book appears to be well written and is to be recommended.

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Segal, Harry L., Rochester, N. Y. (June 10, 1944)
Welch, Paul Brown, Miami, Florida (June 10, 1944)
Williamson, Charles G., Brooklyn, N. Y. (June 10, 1944)
Klein, Capt. Andrew J. V., Ventnor, N. J. (June 10, 1944)

ABSTRACTS OF CURRENT LITERATURE

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MOUTH AND ESOPHAGUS

WEISS, E. Cardiospasm: a psychosomatic disorder. Psychosomatic Med., 6: 58 (Jan.) 1944.

Cardiospasm as a clinical condition is not a common disorder, but because it is such an interesting disease syndrome, it has been widely studied from the anatomical and physiological aspects. The psychic factors in the causation of this disorder have been neglected completely until recently, even though nervousness had been commonly associated with it. We now recognize that psychogenic factors are of extreme importance. The author studied 17 cases of cardiospasm, and in 9 instances a fairly satisfactory psychosomatic analysis was accomplished. The case histories are presented briefly and indicate definitely that psychic factors precipitated the onset of cardiospasm, that psychotherapy was as important as dilatations for alleviation of the condition, and that repeated psychic insults caused exacerbations of the condition. The author emphasizes that the psychic factor is not the whole problem, as this disorder has been found in children but a few days old. "There is undoubtedly an inherent tendency, a predisposition, to which the psychic factor is complementary and it must be that both together, in the majority of cases, are necessary for the development of cardiospasm." These cases are instances of organ neuroses, corresponding to a deeply rooted form of conversion hysteria. Such individuals "cannot swallow." Psychologically, one must attempt to determine what it is that such a patient "cannot swallow" in attempting a therapeutic cure of the cardiospasm.

FRANK NEUWELT.

GARLOCK, J. H. The re-establishment of esophagogastric continuity following resection of esophagus for carcinoma of middle third. Surg., Gyn. Obst., 78: 23 (Jan.) 1944.

Cancer of the middle third of the esophagus

is a serious problem. The operation always employed in cases of this type, until a few years ago, was the one described by Torek in 1913. Lilienthal, Kay, and others have used different methods recently. The author has devised a new method and the first operation performed in May of 1943 was successful. The first operation is given here in detail. In this operation, the entire esophagus up to and including the cardia was resected. The upper two-thirds of the stomach was then transplanted near the apex of the chest and then an anastomosis was performed between the esophageal stump and the stomach, cephalad of the aortic arch near the apex of the chest. The greatest problem in this operation is the blood supply of the two organs that are to be joined together. In the case reported here, the patient was well 6 months after the operation, and could partake of all foods. No cardiovascular symptoms were present at this time.

FRANCIS D. MURPHY.

STOMACH

JONAS, S. The fluoroscopic signs of posterior-wall tumors of the stomach especially those signs developed by palpatory pressure. Rev. Gastroenterol., 11: 27 (Jan.–Feb.) 1944.

The objective of this study is concerned with the examination of fluoroscopic and roentgenologic methods which will further contribute to the diagnosis of posterior wall malignancy of the stomach. Tumors of the anterior wall and of the curvatures manifest themselves in the barium-filled stomach under fluoroscopy by (1) filling defects, irregularly demarcated toward the normal portion of the stomach; (2) by alterations of the peristaltic waves in the curvatures; and (3) by changes in the flexibility of the gastric wall. Moreover, such tumors are usually palpable, while the posterior wall lesion is hidden behind the barium wall and are usually not palpable. The methods which may be employed for fluoroscopic detection of posterior-wall tumors of the stomach are: (1) observation of the filling process; (2) observation of the peristalsis along the curvatures; (3) palpatory pressure with fingers or with the distinctor. The fluoroscopic signs of posterior-wall tumors of the stomach are the following: (1) immediate observation of the diversion and division of the barium flow; (2) appearance of a white barium-free circle on stroking or flat pressure; (3) the latter appears in ulcerating carcinoma remote from the lesser curvature, while those situated near this curvature disclose the meniscus-shaped crater; (4) abrupt termination of the mucosal folds; (5) signs of infiltration, characterized by ragged curvatures, absent peristalsis, rigidity, restricted displacement of contents, and extensive flattening of the lesser curvature. Retrogastric tumors, either primary or secondary, need not confuse the diagnosis when these criteria are carefully considered.

MICHAEL W. SHUTKIN.

ALLEN, A. W. Benign and malignant lesions of the stomach. Bull. N. Y. Acad. Med., 20: 15 (Jan.) 1944.

The differential diagnosis between benign and malignant lesions of the stomach is often impossible. Consequently, all doubtful ulcerations and tumors should be widely resected. This method alone can give patients in the early stages of cancer their greatest chance for cure. Besides, a small percentage of benign ulcers may undergo malignant degeneration. Leiomyomatous tumors are often found to be sarcomatous. Adenomyomatous polyps begin as benign lesions but malignant change occurs in 41%. Local excision of leiomyomata is indicated only when small and in inaccessible regions; otherwise, there should be wide resection. In a series of 225 cases treated as benign gastric ulcer, it was impossible to distinguish clinically between ulcer and carcinoma in 14 per cent. Lesions in the prepyloric and fundal areas were more often found to be malignant than benign. It is impossible to rely on the size of the ulcer as an infallible guide and the finding of free hydrochloric acid does not exclude cancer. In patients over 50 years of age, with symptoms of less than 1 year, the lesion proved to be cancer 5 times as often as benign ulcer. The reverse was true in this age group if symptoms had been present for over 5 years. In younger patients the duration of symptoms did not help in the differential diag-

nosis. Medical treatment of gastric ulcer is less effective than conservative measures for duodenal ulcer. Radical surgery is less dangerous in gastric ulcer than the same type of operation for duodenal ulcer. Finally, attention to the lymphatic spread should be included in operative attempts to cure gastric carcinoma.

ALBERT CORNELL.

BOWEL

DRUECK, C. J. Treatment of chronic ulcerative colitis. Am. J. Dig. Dis., 11: 10 (Jan.) 1944.

The author discusses the importance of rest, sedatives, diet, supportive therapy, and the intravenous administration of calcium gluconate. In his clinical study of 3 cases, sodium iodoxyquinolinesulfonate (anayodin) was chosen because of its definite bacteriostatic action and poor absorbability from the bowel. Anayodin was given in 4-grain doses every 6 hours the first day, 8 grains the second day, and 12 grains for the next 7 days. This was followed by a rest period for 1 week. At the end of the course the diarrhea had usually ceased and the blood and mucus had disappeared from the stool, and there seemed sufficient concentration of the drug in the intestinal tract to maintain definite bacteriostatic action. A rest period of 1 week was allowed to guard against hemolytic anemia or other toxic reactions, and the course of treatments was then repeated a second, third and fourth time. Occasionally, a 2% solution was used as a colonic irrigation. A small amount, about 6 ozs., was introduced into the bowel, retained 3–5 minutes, and allowed to run out.

H. J. SIMS.

BARGEN, J. A. The present status of ulcerative colitis and regional enteritis. Bull. N. Y. Acad. Med., 20: 34 (Jan.) 1944.

In this discussion, the author emphasizes the fact that there are many varieties of ulcerative enterocolitis. Clinically it is most important to determine the responsible etiologic factor in each case. In the streptococcal variety, the diffuse involvement and the typical proctoscopic and roentgenologic pictures, together with the finding of the streptococcus, are important. The finding of endamoeba histolytica is of the greatest importance in the amebic variety. In tuberculous colitis, the presence of the tubercle bacillus, together with the history and finding of tuberculosis elsewhere, is of great value. In the cases caused by bacillary dysentery, the finding of high blood agglutinin fiber, is of significance. The positive Frei reaction and characteristic appearance of the lesions are essential to diagnose those cases due to the virus of venereal lymphogranuloma. In the regional types and groups of unknown cause, such as regional ileitis, continued study is essential. It is important that these be not confused with those forms of ulcerative colitis of specific cause and characteristic features.

ALBERT CORNELL.

POTTER, E. B., AND DOCTER, J. M. Carcinoid tumor of the cecum with metastasis. Am. J. Path., 20: 143 (Jan.) 1944.

To the list of 4 cases of carcinoid of the cecum found in the literature, the authors add a fifth case, that of a 72 year old man who had had gastrointestinal symptoms for years, had frequently been examined in detail, and who finally came to autopsy with the clinical diagnosis of carcinoma of the liver—secondary to an unknown primary site. The primary tumor consisted of a spherical mass, 2.4 cm. in diameter, which arose from the serosa on the medial aspect of the cecum, 8 cm. above the ileo-cecal valve. It had no connection with the appendix, which is the most common site of gastrointestinal carcinoids (85% in 283 recorded cases). The cecal tumor possessed the 3 different types of cells found in carcinoids; namely, (a) round or polyhedral, (b) palisade columnar cells, and (c) prismatic cells which form rosettes around a cavity or vesicle. The cut surface of the tumor was smooth, firm, and of a yellowish brown color. Many regional metastatic lymph nodes in the mesentery revealed similar cells, but the rosette pattern was absent. The liver weighed 1480 gm. and was studded with yellowish nodules throughout both lobes. The nodules varied in size, averaging 6 cm. in diameter. Sections of the

liver showed the same character of cells as those found in the lymph nodes. They were uniformly smaller than the cells found in the primary tumor. Argentaffine granules were demonstrated in the cells of the cecal tumor and in those of the lymph nodes and liver metastases. The authors agree with Cooke and with Mayo and Wilson, who have recorded such carcinoids with metastases, that the term "carcinoma of the carcinoid type" may better be used than the term "carcinoid."

N. W. Jones.

Young, E. L., and Young, E. L. III. Diverticulitis of the colon. New Eng. J. Med., 230: 33 (Jan.) 1944.

In this presentation, the authors review the literature and discuss such factors as incidence, age, sex, etiology, pathogenesis, symptomatology, diagnosis and treatment. In 423 patients studied during 1941 and 1942, barium enema was administered to aid in the diagnosis of abdominal symptoms. Diverticulosis of the colon was demonstrated in 154 patients (36%). In 89 (58%) of these, diverticulitis was shown by X-ray examination. In 43 patients with chronic diverticulitis, there were included those with a clinical and X-ray diagnosis of diverticulitis and a history consistent with diverticulitis together with X-ray evidence of a diverticulum with or without irritability or tenderness or spasm of the colon. In this group, 7 operations were performed (operative incidence of 16%). The authors report 41 cases of acute diverticulitis, of which 85% were between the ages of 40 and 69. Surgical procedures were carried out on 21 patients (51%), with a mortality of 19%. The authors stress the fact that blood was present in the stool in 26% of all cases studied. Conservative treatment, especially the use of X-ray barium by mouth, or where possible by rectum, gives a high percentage of relief.

Irving Gray.

LIVER AND GALLBLADDER

Moschcowitz, E. The electrocardiogram in uncomplicated disease of the gall bladder and the changes induced by operation. J. Mount Sinai Hosp., 10: 632 (Jan.–Feb.) 1944.

Affections of the gall bladder and coronary artery disease are frequently associated. However, even uncomplicated gall bladder disease may affect the electrocardiographic curve, as proven by its restoration to normal after operation. In the majority of cases, the changes represent flattening or inversion of the T waves, and less frequently extrasystoles. A case is reported, the third on record, in which the change was represented by a prolonged PR interval. The mechanism whereby these changes occur is not clear.

Albert Cornell.

Katz, E. Cholecystitis, its diagnosis and treatment. Rev. Gastroenterol., 11: 44 (Jan.–Feb.) 1944.

There is no one categoric routine method of treatment in gall bladder disease because the clinical picture is too often out of proportion to the pathology. Diagnosis is absolutely necessary to establish a basis for either medical or surgical therapy. To this end, a careful history, physical examination, cholecystography, and biliary drainage will contribute greatly. The greatest value of cholecystography lies in the demonstration of a poorly functioning gallbladder with a history of gallbladder disease. Biliary drainage may reveal calcium-bilirubinate masses and cholestrin, which is practically pathognomonic of cholelithiasis. The conservative measures in the treatment of gall bladder disease include: (1) a low fat, well balanced diet; (2) control of constipation; (3) elimination of focal infection; (4) prevention of fatigue and infection; (5) biliary drainage, which may also be practiced postoperatively; (6) choleretics; (7) aperients and saline laxatives; (8) biliary antiseptics; (9) antispasmodics; (10) narcotics, to control colics; and (11) autogenous vaccines. Patients who fail on medical treatment should receive surgery, but only after a thorough study and evaluation of the immediate and postoperative results.

Michael W. Shutkin.

Annegers, J. H., Snapp, F. E., Ivy, A. C., and Atkinson, A. J. Effect of cin-

chophen on secretion of cholic acid. Arch. Int. Med., 73: 1 (Jan.) 1944.

If cinchophen has a direct toxic effect on the liver it should be manifested by a disturbance of secretion of cholic acid, since the output of that substance is readily affected by an infectious or toxic hepatitis. Sixteen experiments were performed on 8 dogs, so prepared that the administered cinchophen could be allowed to undergo continuous enterohepatic circulation. Doses of cinchophen were employed which, on the basis of body weight, are 1 to 4 times the dose recently suggested by Herch for use in the management of gout in humans, and which, in the past have failed to cause disturbance in hepatic liver function as studied by the ordinary tests. Sometimes, these doses caused a marked temporary depression of synthesis and secretion of cholic acid by the livers of dogs. After such doses of cinchophen, a complete temporary suppression of cholic acid may occur in the absence of anorexia and objective gastrointestinal symptoms. Most animals recover from the suppression of synthesis and secretion of cholic acid during repeated administration of cinchophen in the doses used. Death after the administration of cinchophen is due to some vital function of the liver unrelated to the synthesis and excretion of cholic acid or to some general toxic effect not confined to the liver. The suppression of synthesis and secretion of cholic acid is due chiefly to the effect of the drug on the liver and not to its effect on the gastro-intestinal tract. Anorexia is the first and most reliable indication that damage to the liver has occurred sufficient to cause a failure of synthesis and secretion of cholic acid. Susceptibility to cinchophen varies in the same and in different animals.

ALBERT CORNELL.

ENDICOTT, K. M., AND LILLIE, R. D. Ceroid, the pigment of dietary cirrhosis of rats. Am. J. Path., 20: 149 (Jan.) 1944.

Ceroid, a peculiar wax-like pigment, so named by one of the authors, was first found in phagocytes in the cirrhotic livers of rats fed a low protein, low fat diet. Subsequently, it was found in the cells of the liver, lung, spleen, lymph nodes, bone marrow, and adrenal cortex. Its formation was prevented by supplementing the basic diet with choline, methionine, and casein. The chemical nature of it is not wholly known. It has been assumed to be hemofuscin, but the authors have differentiated it from the latter. It has been looked upon as a lipoid conjugated with a protein, and assumed that it may arise from necrotic liver cells. Its presence in cirrhosis, often in fat free liver cells, suggests that it may be a product of altered liver cell metabolism. Again, certain features suggest its origin from neutral fat. However, it is not soluble in ordinary fat solvents, and possesses staining reactions not shared by neutral fat, fatty acids, and the simpler lipoids. Detailed chemical and staining properties of the pigment are given in the paper.

N. W. JONES.

ELIASON, E. L., AND STEVENS, L. W. Acute cholecystitis. Surg., Gyn. Obst., 78: 98 (Jan.) 1944.

The results obtained from a series of 135 cases of acute cholecystitis are presented here. Early surgery was used in all of the cases and the mortality rate was only 1.5%. It is necessary for the surgeon to be very careful in choosing the procedure to be followed. In 68% of the cases presented, cholecystostomy was used and cholecystectomy in the other 32%. In all of the cases subcostal incisions were made. Post operative care is very important if the patient is to recover. The only 2 patients that died in these cases were extremely poor risks to start with. In both fatal cases, cholecystostomies were done. In follow-up studies, all of the patients who had cholecystectomies were well. Twenty-one per cent of the cholecystostomies had second operations and there were no deaths in this second operative group. Eighty per cent of the recurrences occurred within a year after the first operation, so it appears that if the patient is relieved for a year, he has a good chance for permanent relief.

FRANCIS D. MURPHY.

STEVENSON, C. A. Emphysematous cholecystitis. Am. J. Roent. Rad. Therapy, 51: 53 (Jan.) 1944.

Stevenson reports 3 cases of emphysematous

cholecystitis which showed gas in the gall-bladder, blebs in the wall, collection of gas in the pericholecystic tissues, and an absence of gas in the biliary duct system. The condition is rare. Gas bacilli may be found in the bile and walls of the gall bladder. The probable sequence of events in the production of emphysematous cholecystitis is: lodgement of stone in cystic duct, decreased local resistance, allowance of avirulent B. welchii to become virulent, increased dosage of gas bacilli in bile and gall bladder wall, production of gas in gall bladder, emphysematous blebs in the loose areolar connective tissue of the gall bladder wall, and extension of the infection to pericholecystic tissues.

MAURICE FELDMAN.

HUBER, F. Cholecystography and jaundice. Am. J. Roent. Rad. Therapy, 51: 12 (Jan.) 1944.

The author reports the results of cholecystography in 50 unselected jaundice cases. He found no deleterious effects from the dye. In 15 cases with common duct stone, 11 showed a non-filling gall bladder. In 3 cases of cholecystitis without stones, 2 showed a faint shadow and 1 no shadow. In 11 cases of undetermined etiology there was no shadow in 10 cases and in 1 a faint shadow. In 10 cases of toxic and infectious hepatitis, good shadows were obtained in 7 and faint shadows in 3. There were 3 cases of cancer of the pancreas, 1 with a faint gall bladder shadow and 2 with no shadow. In 3 cases of carcinoma of the common duct, 2 revealed a non-filling gall bladder and 1 a faint shadow. In 2 cases of carcinoma of the liver, 1 filled, the other did not. In 1 case of cirrhosis of the liver there was a non-filling. In 1 case of duodenal ulceration associated with jaundice, there was a non-filling gall bladder. Huber attempted to distinguish surgical from medical cases by this procedure. He found this possible in 36 cases where the jaundice was decreasing. However, when the jaundice was increasing, the test is of no value.

MAURICE FELDMAN.

MIRSKY, I. A., VON BRECHT, R., WILLIAMS, L. D. Hepatic dysfunction in malaria. Science, 99: 20 (Jan.) 1944.

It has never been generally acknowledged that liver dysfunction is usually present in malaria. Ten patients are reported here in varying stages of malaria. They were given the cephalin cholesterol flocculation test and it was positive in all 10 cases. This indicates the presence of hepatic damage. In some cases the tests were done before the atabrine or quinine were given, and because of this it is probable that the quinine and atabrine were not responsible for the damage. In malaria then, it is necessary to treat the liver and to try to bring it back to normal as well as to treat the malaria itself. In addition to administering the usual drugs given during malaria, high carbohydrate, high protein, and high vitamin diets should be used.

FRANCIS D. MURPHY.

GRAHAM, R. L. Sudden death in young adults in association with fatty liver. Bull. Johns Hopkins Hosp., 74: 16 (Jan.) 1944.

This report includes 5 recent cases, with mention of 6 others. Oddly, none of the cases occurred between the period of late June and late September. Six cases were excluded from the report because of the existence of other associated lesions. A history of alcoholism was given by 3, and suspected in the fourth. Three had attacks of unconsciousness, and 1 had vague symptoms of weakness and anorexia for several months prior to death. In another, death occurred during sleep. Microscopic examination showed a similar uniformity. In 3 cases, each liver cell was distended with a fat globule. In the other 2 cases the picture was only slightly less marked. The striking feature is the suddenness of death. Four of these cases closely simulated a coronary death, yet, the most careful search showed no demonstrable heart lesion. Graham suggests that vitamin deficiency, with or without hypoglycemia, might be a contributing factor.

H. J. SIMS.

PANCREAS

UMANSKY, A. L. Subtotal pancreatectomy for hypoglycemia. J. Mount Sinai Hosp., 10: 698 (Jan.–Feb.) 1944.

The author reports a case in which all the

criteria for diagnosis of islet cell tumor were satisfied. Despite careful exploration of the pancreas, no tumor was found and a subtotal pancreatectomy was done. Microscopically, normal pancreatic tissue was found, but the patient continued to have attacks of hypoglycemia postoperatively. It is planned to reexplore the patient in the hope of demonstrating an adenoma of the remaining portion of the pancreas. It would seem from the literature and from this case (although unproved) that in the presence of an adenoma, regardless of its dimensions, or where some extrapancreatic factor is responsible, symptoms of hyperinsulinism will persist no matter how much pancreatic tissue is removed. Until a definitive method for differentiating organic from functional abnormalities of the islands of Langerhans is found, especially those due to imbalance between interrelated endocrine organs, disappointing results will be obtained.

ALBERT CORNELL.

ULCER

RAW, S. C. Perforation of gastric and duodenal ulcers. Lancet, 246: 12 (Jan.) 1944.

The author records the experiences he gained and the results he obtained in a personal series of 312 cases of perforation of gastric and duodenal ulcers. (1) In atypical cases, perforation is sometimes closely simulated by such conditions as coronary thrombosis, pleurisy, cholecystitis, pancreatitis, perforated appendicitis, renal colic, and obstruction of the small bowel. (2) Before operation, at least 60% of the cases have pain referred to one or both supraclavicular regions, due to irritation of the under-surface of the diaphragm by gastric contents or bile. In the author's experience the clinical sign of diminished liver dullness is dangerous and misleading. He states that it is present only in obvious cases and one must take account of variations in normal size of the liver, paralytic distension, intestinal obstruction and emphysema of the lungs. (3) The pulse rate and temperature remain normal for only a few hours and are of little help in distinguishing a 24-hour perforation from any other peritonitis. (4) A combination of upper and lower abdominal rigidity usually indicates a primary upper abdominal peritonitis, particularly if the rigidity is greater on the right than on the left. In doubtful cases the persistence of right upper rectus rigidity after the pain has been somewhat relieved by morphine will aid the diagnosis. (5) Nearly all subphrenic abscesses following perforation are on the right side, and it is common to find abscess cavities beneath the diaphragm and between the duodenum and liver at the same time. These can often be drained together through a subcostal incision under local anesthesia. Stress is placed on the aphorism of Rutherford Morison; "pus somewhere, pus found nowhere—therefore, subphrenic abscess". (6) The author makes the following general comments: the fatality-rate runs closely parallel to the number of hours between perforation and operation; advancing years make the prognosis worse; perforations in women are uncommon and a trap to the unwary; the immediate operative mortality can be reduced by local anesthesia and intravenous blood-plasma in selected cases.

DAVID J. SANDWEISS.

SPICER, C. C., STEWART, D. N., WINSER, D. M. DE R. Perforated peptic ulcer during the period of heavy air-raids. Lancet, 246: 14 (Jan.) 1944.

The authors have previously published data from 16 London hospitals demonstrating a rise in the incidence of perforation in peptic ulcer during the first 4 months of the heavy air raids on London. To confirm the belief that this rise was no mere artefact, the authors present additional figures for the entire raid period together with those for the 18 months following the raids, using the admissions of the same 16 London hospitals. The purpose of the paper was not so much to show that anxiety might be an important cause in the perforation, but primarily to place the increase of perforations during the air raids on a firm statistical foundation. The authors show that (1) the increase in perforated peptic ulcer during the period of heavy raiding was statistically significant when compared with the previous 3 and the following 2 years; (2) statistical evidence is in favor of some general tendency having operated during the air raid period to cause

perforation, and of some other, or less active, general tendency operating in the 2 following years; and (3) there is also a significant increase in perforation during the month of December.

DAVID J. SANDWEISS.

IVY, A. C. Some recent developments in the physiology of the stomach and intestine which pertain to the management of peptic ulcer. Bull. N. Y. Acad. Med., 20: 5 (Jan.) 1944.

Gastric secretion and motility can be inhibited by the action of enterogastrone, which is formed in the mucosa of the upper intestine. However, the principle responsible for inhibiting gastric secretion is different from that which inhibits gastric motility, as recent experiments show. The urine of man and dog also contains inhibitors of gastric secretion and motility, which are called urogastrone. Significantly, patients with peptic ulcer excrete less urogastrone than non-peptic ulcer subjects. It has been suggested that the urinary substances represent excreted enterogastrone. There is a urogastrone which is not identical with the latter; this was shown by recent studies with pepsin, which inactivates enterogastrone while having no effect on the urogastrone. Using enterogastrone, it has been possible to "immunize" Mann-Williamson dogs against gastro-jejunal ulcer. Since it apparently does not act by depressing gastric secretion or abolishing pepsin production, it is possible that enterogastrone injections act by increasing the resistance of the mucosa to ulceration. Palliative results were obtained in 15 patients with peptic ulcer treated with the enterogastrone preparation, which incidentally, does not inhibit motility in the dosage used. From the animal experiments, it is hoped that in time it may be possible to "immunize" patients against repeated recurrences of peptic ulcer. From other studies, the author concludes that the use of alcoholic beverages, excessive smoking and excessive use of coffee so affect the gastric mucosa and glands as to predispose to gastroduodenal ulceration in susceptible persons.

ALBERT CORNELL.

PROCTOLOGY

KLEIN, I. Roentgen study of lymphogranuloma venereum. Am. J. Roent. Rad. Therapy, 51: 70 (Jan.) 1944.

The author describes 24 cases of lymphogranuloma venereum. The condition runs a chronic course assuming variable forms and is occasionally mistaken for cancer. The lesion begins at the anal region and tends to encircle the wall of the rectum. The condition produces a rectal stricture above the anal orifice and an ulcerating, granulating lesion of the rectum. It causes tenesmus, constipation, mucus and blood in the stools. The roentgen examination shows evidence of destruction of the mucous membrane, rectal strictures, distention of the rectal pouch, and occasionally fistulous tracts. The author gives in detail the differential diagnosis between this condition and cancer.

MAURICE FELDMAN.

SURGERY

HICKEN, N. F., CORAY, Q. V., AND CARLQUIST, J. H. A new technique for using the Levine tube in biliary intestinal anastomoses. Surg., Gyn. Obst., 78: 58 (Jan.) 1944.

The results from using the indwelling Levine tube for decompressing an obstructed biliary tree in 11 cases are given here. Four cases are reported in detail. There were only 2 operative deaths—one resulting from massive pulmonary embolus and the other from hepatic insufficiency. In these operations, the Levine tube is passed into the stomach just before the operation is started. The tube is pulled through the gastric incision and inserted well into the lumen of the gall bladder cavity and is anchored there. An anastomosis is made around the catheter. The bile ducts are kept decompressed by continuous suction. The tube is usually removed on the 7th to the 10th post-operative day if the bile ducts are again of normal size and tone. The bile flows into this segment as soon as the tube is removed. This method has been used successfully in cholecystenterostomies, choledochoenterostomies, and hepaticoenterostomies. Its further use is recommended by the excellent results obtained so far.

FRANCIS D. MURPHY.

PRIESTLEY, J. T., THOMPSON, L., AND SEALY, W. B. Bacteriologic aspects of gastric contents in presence of surgical lesions of the stomach and duodenum. Proc. Staff Meet. Mayo Clinic, 19: 1 (Jan.) 1944.

It is generally agreed that the contents of the normal fasting stomach are sterile. However, this may not be so in the presence of various types of gastric lesions, and the bacterial contents of the stomach may become of importance in their surgical treatment. Forty one patients were studied, 39 of whom had had resections performed and the other 2 had been gastroenterostomized. At the time of operation gastric contents were aspirated and cultures made on blood agar and Endo's agar. Gastric acidity was determined either pre-operatively or from the stomach contents at time of operation. The stomach in each case had been lavaged before operation. Twenty four of the cultures showed no growth, and 17 of them revealed the presence of one or more organisms. Cultures seldom grew when the gastric acidity had been 40 clinical units or greater. Growth of organisms also depended to some extent upon the type of gastric lesions as well as the level of acidity. Cultures were positive in but 4 of 22 cases of duodenal ulcer; micrococci were present in 2 and green producing streptococci in 2 others. In each of 5 cases in which resection for a malignancy was performed, cultures were positive. Not one of these cases had any free HCl. Cultures were positive also in 6 out of 7 cases in which resection was performed for gastric ulcer, but in none of these was the total acid as high as 40 C.U. These findings are of interest in relation to the necessity for the use of sulfa drugs in cases of gastric surgery, aseptic anastomoses, preoperative gastric lavage, etc.

FRANK NEUWELT.

PHYSIOLOGY: SECRETION

THOMAS, J. E., AND CRIDER, J. O. Specific gravity and total nitrogen of pancreatic juice secreted in response to various stimuli. Am. J. Physiol., 140: 574 (Jan.) 1944.

The specific gravity and total nitrogen of dog's pancreatic juice vary with the type of stimulus used to provoke secretion. Peptone in the intestine causes the most concentrated secretion, soap causes a less concentrated secretion, and HCl the most dilute secretion. The secretion caused by intravenous administration of "Pancreotest" resembles that caused by HCl in the intestine.

ARTHUR E. MEYER.

METABOLISM AND NUTRITION

MCINTOSH, R. Disorders of the digestive system leading to vitamin deficiency states in infants and children. Bull. N. Y. Acad. Med., 20: 25 (Jan.) 1944.

Clinical deficiencies of fat soluble vitamins A and K are seen in conditions in which there is a disturbance of absorption of food fat. These include diseases of the liver and bile ducts which impair the production and excretion of bile, conditions which lead to inadequate delivery of pancreatic enzymes into the intestinal lumen, and rarely, to diseases which directly affect the intestinal mucosa at the site of fat absorption, interfering with the transmission of lipoids through the gut wall. The importance of congenital pancreatic fibrosis in producing vitamin deficiency is emphasized. Pancreatic insufficiency may make itself known in various guises: meconium ileus in early infancy, retarded growth, or as chronic bronchitis, sometimes with bronchiectoses and pneumonitis, in the first 6 months. From the age of 6 months on, it appears under the mask of the celiac syndrome. Vitamin A deficiency occurs more in the pancreatic disorders than in those of liver or intestine. Vitamin K deficiency occurs more often in hepatic disease, as in obstructive jaundice. The water-soluble ascorbic acid and Vitamin B-complex factors are also discussed. Knowing the possible harmful effects of vitamin deficiencies, it is important to keep their possible risks in mind and to treat the patient accordingly while the fight against the fundamental disease is going on. This is especially important since the evidences of vitamin deficiency may develop insidiously and may not be recognized until too late for regression or repair.

ALBERT CORNELL.

KELLY, H. T., AND SHEPPARD, M. The incidence of deficiency syndromes. N. Y. State J. Med., 44: 172 (Jan.) 1944.

Two hundred and twenty-five patients of upper income levels were studied for evidence of deficiency states. A detailed medical and nutritional history was taken and a complete physical examination performed. Many routine laboratory examinations and diagnostic tests for specific vitamin and mineral deficiencies were undertaken, as well as X-ray investigation of the gastro-intestinal tract. The cause of nutritional failure may be found in inadequate diet, or in interference with the absorption and assimilation of nutritional factors. In order to treat nutritional failure successfully, the physician must recognize this condition and then determine if the cause is exogenous or endogenous.

PHILIP LEVITSKY.

PHARMACOLOGY

BAROWSKY, H., AND BOYD, L. J. The use of garlic (allisatin) in gastrointestinal disturbances. Rev. Gastroenterology, 11: 22 (Jan.–Feb.) 1944.

Ancient and middle age manuscripts have often alluded to the action of garlic on the alimentary tract. It has been used in this century prophylactically for gastric and intestinal maladies, amebic dysentery, cholera, and as an anthelmintic. As yet no explanation is forthcoming for the varied effects reported (such as spasmolysis, sedation, and vagal action) nor has the active principle responsible for these effects been identified. This report is limited to 50 patients observed after treatment with a garlic-charcoal preparation (allisatin); of these, 15 had organic gastro-intestinal disease ranging from gastric carcinoma to ulcerative colitis, 11 were cases of functional dyspepsia, 6 had chronic cholecystitis, and 18 presented reflex gastroenteric problems. All patients received 2 to 3 tablets of allisatin 3 times daily for one week, and then 1 or 2 tablets 3 times a day. The most conspicuous benefit was the relief of intestinal and gastric flatulence, particularly in the group with cardio-vascular disease. Patients with pulmonary tuberculosis were relieved of nausea, vomiting, flatulence and distention. No untoward effects were noted, and the preparation was not recognized by its odor.

MICHAEL W. SHUTKIN.

ANATOMY

ANDREWS, W. Senile changes in the pancreas of Wistar Institute rats and of man with special regard to the similarity of locule and cavity formation. Am. J. Anat., 74: 97 (Jan.) 1944.

Andrew presents a comparative study of the senile changes in the rat and human pancreas. Seventy-four rats and 55 human cases were studied. In the rat the pancreas showed an increase in the number and proliferation of epithelial cells of the interlobar and intralobar ducts. Most important of the duct-cell proliferation is an apparent invasion of the secreting tissue of the lobule of the duct epithelium. In some of the senile animals the proliferation is so extensive that great masses of cells with clear nuclei are present. In advanced cases the alveoli show degenerative changes. Metaplasia in the interlobular ducts is only one of the manifestations of proliferation. Saccular cavities forming relatively large irregular spaces may be seen in late stages. Andrews was not able to find any definite degenerative changes in the islets of Langerhans, but atrophy occurs as a secondary phase. In the human subject, the majority of the pancreases also contained spheroidal or ovoidal cavities. These cavities or locules were more numerous in the older age group. This tendency to cavity formation presents the conspicuous difference between the senile and younger age groups. The locules in the human resemble those in the rat. The conversion of the lobules into cavities is characteristic of senile changes and indicates a decrease in function of the exocrine portion of the gland in the aged.

MAURICE FELDMAN.

MISCELLANEOUS

SHEEHAN, D. Physiological mechanisms involved in gastrointestinal dysfunction. Psychosomatic Med., 6: 56 (Jan.) 1944.

Every reaction of an organism, or of its parts, to a new stimulus is superimposed upon a baseline which itself is fluctuating and which is a reflection of the organism's response to

an ever changing environment. The induction, the observation, and the recording of such experimentally produced procedures may be extremely variable and difficult, even when confined to a system so long and so well studied as the gastro-intestinal tract. In general, the effects of sympathetic and parasympathetic stimuli are known, but frequently both systems are called into play simultaneously in a selective manner. Autonomic reactions often go on independent of somatic or voluntary stimuli; on the other hand they are often influenced by the latter as well. Fundamentally, from a strictly physiological view, an interdependence exists between these systems. It is these autonomic adjustments which allow for the "milieu interieur" of Claude Bernard, or what Cannon has aptly termed, "homeostasis". An autonomic response invoked in the interest of homeostasis or as an expression of emotional behaviour may become excessive, giving rise to what have unfortunately been termed "functional" states or illnesses. Such functional disturbances, exaggerations of normal physiological fluctuations, may lead to actual pathological changes.

FRANK NEUWELT.

SNAPPER, I. Salmonellosis caused by the ingestion of ducks' eggs. Am. J. Dig. Dis., 11: 8 (Jan.) 1944.

In Western Europe, the 2 species of *Salmonella* likely to be found in ducks' eggs are *S. enteritidis* and *S. typhimurium*. In the United States, *S. typhimurium* was found in 176 of 223 cultures derived from 100 outbreaks of avian Salmonellosis. Twenty-two of these cultures were obtained in 5 outbreaks of Salmonellosis of ducks, 3 of which outbreaks were caused by *S. typhimurium*, 1 by *S. anatis*, and one by *Salmonella sp.* *S. enteritidis* has also been recovered from the stools of ducks in the United States. Salmonellosis of human beings, arising from the consumption of eggs from ducks attacked by species of *Salmonella*, is of common occurrence in Western Europe. In the United States outbreaks of Salmonellosis of human beings caused by the use of infected ducks' eggs are rare, but one such outbreak occurred in Kansas.

H. J. SIMS.

ENGELHARDT, H. T., AND DERBES, V. J. Allergy to liver extract. Southern Med. J., 37: 31 (Jan.) 1944.

The authors report 2 illustrative cases of allergy to liver extract. In one, there were pronounced local reactions following the continued use of iron and concentrated liver extract in the treatment of a young patient suffering from a grade of hypochromic and microcytic anemia. The injections in the outer aspect of the arm were complicated by local reactions manifest by pronounced edema, as treatment was continued. Within 72 hours after discontinuance of liver therapy, the arm returned to normal. In the second case, following the first injection of liver extract, the patient became weak, had difficulty in breathing, and lost consciousness. It was subsequently learned that the patient had had similar reactions to the administration of liver extract previously. Atopic reagin antibodies to liver extract were found in the blood, as proved by passive transfer studies on 3 non-allergic or non-atopic individuals. The authors suggest that the local type of allergic reaction may be avoided by alternating the site of injection. There is a brief review of the various types of reaction to parenteral liver therapy.

IRVING GRAY.

LEVINE, S., AND SOLIS-COHEN, L. Survey film diagnosis of acute surgical abdomen. Surg., Gyn. Obst., 78: 76 (Jan.) 1944.

It is often difficult to diagnose correctly intra-abdominal surgical conditions. Aid in the diagnosis of these problems can be obtained through survey films or flat plates of the abdomen. At least 3 films should be taken, including a high and a low supine film and an upright film. Other positions are helpful if they can be obtained. These films often reveal conditions that otherwise could not be determined accurately, and they often help in reaching a precise conclusion in baffling cases. Five cases are reported in detail.

FRANCIS D. MURPHY.

GLASER, K., AND BRUCE, J. W. Treatment of epidemic diarrhea and dysenteries in infants and young children. J. Pediatrics, 24: 53 (1944).

A large series of infantile gastro-enteritis cases was treated in the Louisville General Hospital between 1938 and 1942. During the last two of these years, a new method of feeding was put on trial and found successful, having been applied without modification in both epidemic diarrhea and bacillary dysentery cases. The main principles of treatment consisted of: (1) a starvation period of twelve hours; (2) oral and intravenous hydration and combat of acidosis: (3) feeding of buttermilk, skimmed boiled milk, or protein milk in 3 to 4 hourly intervals, the amount being regulated entirely by the appetite of the patient; (4) sulfathiazole and sulfaguanidine administration; (5) plasma and blood transfusions; (6) specific antiserum therapy; and (7) bismuth and paregoric, but only in the treatment of resistant patients. This new method decreased the average hospitalization time, the total number of deaths, and the death rate. The infants took large amounts of milk with each feeding, regulating their intake according to appetite. Their care on the hospital ward was thereby simplified, and protection was secured against undesirable effects of inanition.

IRVING WOLMAN.

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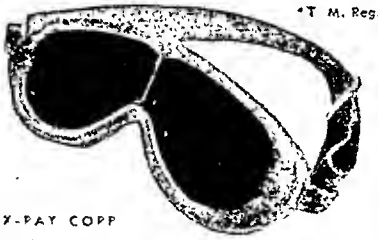

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* Underwood, G.M.: Gastro-Intestinal Tuberculosis. Texas St. J. Med., 40: 14-17 (May) 1944

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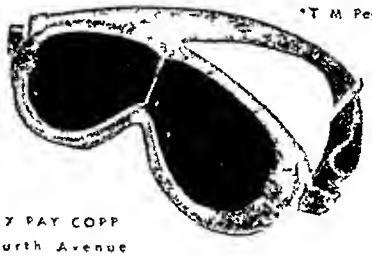

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